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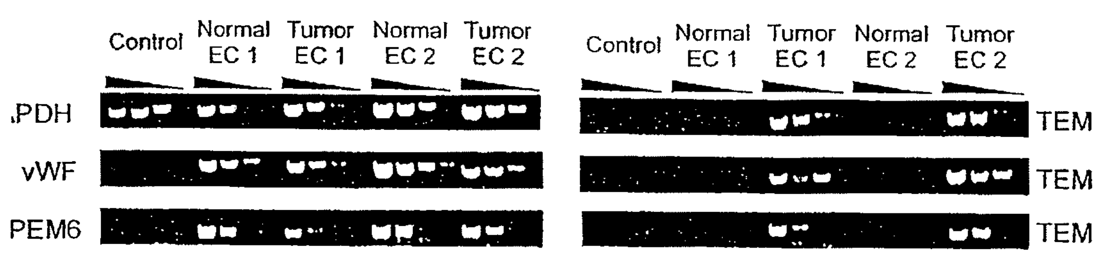
(54) Title: ENDOTHELIAL CELL EXPRESSION PATTERNS



(57) Abstract: To gain a better understanding of tumor angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived from normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and tumor-derived endothelium revealed 79 differentially expressed genes, including 46 that were specifically elevated in tumor-associated endothelium. Experiments with representative genes from this group demonstrated that most were similarly expressed in the endothelium of primary lung, breast, brain, and pancreatic cancers as well as in metastatic lesions of the liver. These results demonstrate that neoplastic and normal endothelium in humans are distinct at the molecular level,

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ENDOTHELIAL CELL EXPRESSION PATTERNS

[01] This application claims the benefit of provisional applications serial number 60/282,850 filed April 11, 2001, and 60,308,829 filed August 1, 2001, the disclosures of which are expressly incorporated herein.

[02] The U.S. government retains certain rights in the invention by virtue of the provisions of National Institutes of Heath grants CA57345 and CA43460, which supported this work.

TECHNICAL FIELD OF THE INVENTION

[03] This invention is related to the area of angiogenesis and anti-angiogenesis. In particular, it relates to genes which are characteristically expressed in tumor endothelial and normal endothelial cells.

BACKGROUND OF THE INVENTION

[04] It is now widely recognized that tumors require a blood supply for expansive growth. This recognition has stimulated a profusion of research on tumor angiogenesis, based on the idea that the vasculature in tumors represents a potential therapeutic target. However, several basic questions about tumor endothelium remain unanswered. For example, are vessels of tumors qualitatively different from normal vessels of the same tissue? What is the relationship of tumor endothelium to endothelium of healing wounds or other physiological or pathological forms of angiogenesis? The answers to these questions critically impact on the potential for new therapeutic approaches to inhibit angiogenesis in a specific manner.

[05] There is a continuing need in the art to characterize the vasculature of tumors relative to normal vasculature so that any differences can be exploited for therapeutic and diagnostic benefits.

[06] One technique which can be used to characterize gene expression, or more precisely gene transcription, is termed serial analysis of gene expression (SAGE). Briefly, the SAGE approach is a method for the rapid quantitative and qualitative analysis of mRNA transcripts based upon the isolation and analysis of short defined sequence tags (SAGE Tags) corresponding to expressed genes. Each Tag is a short nucleotide sequences (9-17 base pairs in length) from a defined position in the transcript. In the SAGE method, the Tags are dimerized to reduce bias inherent in cloning or amplification reactions. (See, US Patent 5,695,937) SAGE is particularly suited to the characterization of genes associated with vasculature stimulation or inhibition because it is capable of detecting rare sequences, evaluating large numbers of sequences at one time, and to provide a basis for the identification of previously unknown genes.

SUMMARY OF THE INVENTION

[07] One embodiment of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an in tact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[08] According to another embodiment of the invention a method of inhibiting neoangiogenesis is provided. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a subject in need thereof. Neoangiogenesis is consequently inhibited. The subject may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, may have psoriasis, for example.

[09] Another aspect of the invention is a method of inhibiting tumor growth. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, 22, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, and 271, respectively, is administered to a human subject bearing a tumor. The growth of the tumor is consequently inhibited.

[10] Still another aspect of the invention provides an isolated molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 200, 212, 230, 232, and 271, respectively. The molecule can be, for example, an in tact antibody molecule, a single chain variable region (ScFv), a monoclonal antibody, a humanized antibody, or a human antibody. The molecule can optionally be bound to a cytotoxic moiety, bound to a therapeutic moiety, bound to a detectable moiety, or bound to an anti-tumor agent.

[11] According to still another aspect of the invention an isolated and purified human transmembrane protein is provided. The protein is selected from the group consisting of: TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively.

[12] Yet another aspect of the invention is an isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The isolated and purified nucleic acid molecule may optionally comprise a coding sequence selected from those shown in SEQ ID NO: : 199, 211, 229, and 231.

[13] Still another aspect of the invention is a recombinant host cell which comprises a nucleic acid molecule. The nucleic acid molecule comprises a coding sequence for a transmembrane TEM selected from the group consisting of: : TEM 3, 9, 17, and 19 as shown in SEQ ID NO: 200, 212, 230, and 232, respectively. The recombinant host cell optionally comprises a coding sequence selected from those shown in SEQ ID NO: 199, 211, 229, and 231.

[14] According to one embodiment of the invention a method is provided for inducing an immune response in a mammal. A nucleic acid molecule comprising a coding sequence for a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: , respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal. Optionally the coding sequence is shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271.

[15] According to yet another embodiment of the invention a method of inducing an immune response in a mammal is provided. A purified human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 13, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250 and 271, respectively, is administered to the mammal. An immune response to the human transmembrane protein is thereby induced in the mammal.

[16] Another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with an isolated and purified human trasmembrane protein selected from the group consisting of 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271. The isolated and purified human trasmembrane protein is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 30, 19, and 44 as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 250, and 271 respectively. Binding of the molecule comprising an antibody variable region to the human transmembrane protein is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

[17] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a cell comprising a human transmembrane protein selected from the group consisting of 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232. The cell is also contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, and 19 as shown in SEQ ID NO: 196, 200, 212, 230, and 232 , respectively. Binding of the molecule comprising an antibody variable region to the cell is determined. A test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

[18] Yet another aspect of the invention is a method for identification of a ligand involved in endothelial cell regulation. A test compound is contacted with a human transmembrane protein selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29,

40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275. Binding of a test compound to the human transmembrane protein is determined. A test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

[19] Another embodiment of the present invention is a soluble form of a human transmembrane protein selected from the group consisting of: TEM 1, 3, 9, 17, 19, 22, 30, and 44 as shown in SEQ ID NO: 196, 200, 212, 230, 232, 238, 250, and 271 respectively. The soluble forms lack transmembrane domains. The soluble form may consist of an extracellular domain of the human transmembrane protein.

[20] Also provided by the present invention is a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is adminstered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[21] Another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A soluble form of a human transmembrane protein is administered to the patient. Neoangiogenesis in the patient is consequently inhibited. The patient may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy, may have rheumatoid arthritis, or may have psoriasis, for example.

[22] According to still another aspect of the invention a method of identifying regions of neoangiogenesis in a patient is provided. A molecule comprising an antibody variable region which specifically binds to an extracellular

domain of a TEM protein selected from the group consisting of: 1, 3, 9, 13, 17, 19, 22, 30, and 44, as shown in SEQ ID NO: 196, 200, 212, 220, 230, 232, 238, 250, and 271, respectively, is administered to a patient. The molecule is bound to a detectable moiety. The detectable moiety is detected in the pateint, thereby identifying neoangiogenesis.

[23] According to another aspect of the invention a method is provided for inducing an immune response to tumor endothelial cells in a patient. A mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 13, 17, 19, 22, and 30 as shown in SEQ ID NO: 291, 293, 299, 295, 303, 297, 301, 305, and 307, is administered to a patient in need thereof. An immune response to a human TEM protein is consequently induced.

[24] Still another embodiment of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is contacted with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 1, 3, 9, 17, 19, and 44, as shown in SEQ ID NO: 196, 200, 212, 230, 232, and 271, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neo-angiogenesis in the patient.

[25] Still another embodiment of the invention provides a method of inhibiting neoangiogenesis in a patient. A molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 and 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, is administered to the patient. Neoangiogenesis in the patient consequently inhibited.

[26] Yet another aspect of the invention is a method of screening for neoangiogenesis in a patient. A body fluid collected from the patient is

contacted with a molecule comprising an antibody variable region which specifically binds to a TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, respectively. Detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

[27] Also provided by the present invention is a method of promoting neoangiogenesis in a patient. A TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, is administered to a patient in need of neoangiogenesis. Neoangiogenesis in the patient is consequently stimulated.

[28] One embodiment of the invention provides a method of promoting neoangiogenesis in a patient. A nucleic acid molecule encoding a TEM protein selected from the group consising of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264, is administered to a patient in need of neoangiogenesis. The TEM protein is consequently expressed and neoangiogenesis in the patient is stimulated.

[29] Another embodiment of the invention provides a method of screening for neoangiogenesis in a patient. A TEM protein selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40, as shown in SEQ ID NO: : 202, 206, 208, 214, 218, 223 & 224, 234, 242, 244, 252, 257, 259, 261. 263, and 265, respectively, is detected in a body fluid collected from the patient. Detection of the TEM protein indicates neoangiogenesis in the patient.

[30] Another aspect of the invention is a method of screening for neoangiogenesis in a patient. A nucleic acid encoding a TEM protein

selected from the group consisting of: 4, 6, 7, 10, 12, 14, 20, 25, 27, 31, 36, 37, 38, 39, and 40 is detected in a body fluid collected from the patient. The nucleic acid is selected from the group consisting of those shown in SEQ ID NO: 201, 205, 207, 213, 217, 221 & 222, 233, 241, 243, 251, 256, 258, 260, 262, and 264. Detection of the TEM protein indicates neoangiogenesis in the patient.

[31] Yet another embodiment of the invention is an isolated and purified nucleic acid molecule which encodes a NEM protein selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. The nucleic acid molecule optionally comprises a coding sequence as shown in SEQ ID NO: 278, 282, 284, and 288. The nucleic acid may be maintained in a recombinant host cell.

[32] The present invention also provides an isolated and purified NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[33] The present invention further provides an isolated molecule comprising an antibody variable region which specifically binds to a NEM protein selected from the group consisting of: 14, 22, 23, and 33, as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289.

[34] An additional embodiment of the present invention is a method of inhibiting neoangiogenesis. An effective amount of a NEM protein selected from the group consising of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289 is administered to a subject in need thereof . Neoangiogenesis is thereby inhibited.

[35] A still further embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM genes selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14,

15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: : 195, 197, 199, 201, 203, 205, 207, 209, 211, 213, 215, 217, 221 & 222, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, 255, 256, 258, 260, 262, 266, 268, 270, 272, and 274, respectively, are contacted with a test compound. Expression of said one or more TEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Test compounds which increase expression can be identified as candidates for promoting wound healing.

[36] Yet another embodiment of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. The amount of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the amount of one or more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Alternatively, a test compound which increases the amount of one or more TEM proteins in said cells is identified as a candidate drug for treating wound healing.

[37] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more TEM proteins selected from the group consisting of: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 196, 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively, are contacted with a test compound. Activity of said one or more TEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it decreases the activity of one more TEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs. Optionally the cells are endothelial cells. If a test compound increases the acitivity of one more TEM proteins in said cells it can be identified as a candidate drug for treating wound healing.

[38] An additional aspect of the invention is a method to identify candidate drugs for treating patients bearing tumors. A test compound is contacted with recombinant host cells which are transfected with an expression construct which encodes one or more TEM proteins selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 40, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275, respectively. Proliferation of said cells is determined. A test compound which inhibits proliferation of said cells is identified as a candidate drug for treating patients bearing tumors. A test coumpound which stimulates proliferation of said

cells is identified as a candidate drug for promoting neoangiogenesis, such as for use in wound healing.

[39] Another embodiment of the invention provides a method to identify candidate drugs for treating tumors. Cells which express one or more NEM genes selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 278, 282, 284, and 288, respectively, are contacted with a test compound. Expression of said one or more NEM genes is determined by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA. A test compound is identified as a candidate drug for treating tumors if it increases expression of said one or more NEM genes. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[40] According to another aspect of the invention a method is provided to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. The amount of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it increases the amount of one more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[41] An additional aspect of the invention is a method to identify candidate drugs for treating tumors. Cells which express one or more NEM proteins selected from the group consisting of: 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, are contacted with a test compound. Activity of said one or more NEM proteins in said cells is determined. A test compound is identified as a candidate drug for treating tumors if it

increases the activity of said one or more NEM proteins in said cells. Optionally the cells are endothelial cells. Alternatively or additionally, the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more NEMs.

[42] Still another embodiment of the invention provides a method to identify candidate drugs for treating patients bearing tumors. Atest compound is contacted with recombinant host cells which are transfected with an expession construct which encodes one or more NEM proteins selected from the group consisting of 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289. Proliferation of said cells is determined. A test compound which stimulates proliferation of said cells is identified as a candidate drug for treating patients bearing tumors.

[43] Another aspect of the invention is a method for identifying endothelial cells. One or more antibodies which bind specifically to a TEM or NEM protein selected from the group consisting of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with a population of cells. Cells in the population which have bound to said antibodies are detected. Cells which are bound to said antibodies are identified as endothelial cells. Optionally cells which have bound to said antibodies are isolated from cells which have not bound.

[44] Still another aspect of the invention is a method for identifying endothelial cells. One or more nucleic acid hybridization probes which are complementary to a TEM or NEM gene nucleic acid sequence selected from the group consisting of of TEM : 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16,

17, 19, 20, 21, 22, 24, 25, 27, 28, 29, 30, 31, 33, 35, 36, 37, 38, 39, 41, 42, 44, 45, and 46 as shown in SEQ ID NO: 198, 200, 202, 204, 206, 208, 210, 212, 214, 216, 218, 223 & 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250, 252, 254, 358, 257, 259, 261, 263, 267, 269, 271, 273, and 275 and NEM 14, 22, 23, and 33 as shown in SEQ ID NO: 279, 283, 285, 286, 287, and 289, is contacted with nucleic acids of a population of cells. Nucleic acids which have specifically hybridized to said nucleic acid hybridization probes are detected. Cells whose nucleic acids specifically hybridized are identified as endothelial cells.

[45] Yet another embodiment of the invention is a method of inhibiting neoangiogenesis. An effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 17, and 19, as shown in SEQ ID NO: 291, 293, 299, 295, 297, and 301, respectively, is administered to a subject in need thereof . Neoangiogenesis is thereby inhibited. The subject may be a mouse, may bear a vascularized tumor, may have polycystic kidney disease, may have diabetic retinopathy. may have rheumatoid arthritis, or may have psoriasis, for example.

[46] These and other embodiments which will be apparent to those of skill in the art upon reading the specification provide the art with reagents and methods for detection, diagnosis, therapy, and drug screening pertaining to neoangiogenesis and pathological processes involving or requiring neoangiogenesis.

BRIEF DESCRIPTION OF THE DRAWINGS

[47] Fig. 1A-1B. vWF expression in colorectal cancers. vWF (red stain) was detected in vessels by in situ hybridization. At low power magnification (Fig. 1.A) vessels were often surrounded by a perivascular cuff of viable cells

(red arrows), with a ring of necrotic cells evident at the periphery (black arrows). At high power magnification (Fig. 1.B) the expression of vWF (red) was clearly localized to the vessels. Sections were counterstained with methyl green.

[48] Fig. 2A-2D. Purification of Endothelial Cells (ECs) from human normal and malignant tissue. (Fig. 2A) Vessels (red) of frozen sections were stained by immunofluorescence with the P1H12 monoclonal antibody (Chemicon, Temecula, CA) and detected using a biotinylated goat anti-mouse IgG secondary antibody followed by rhodamine-linked strepavidin. The region stained is from within the lamina propria of normal colonic mucosa. Note that the larger vessels (arrowheads) and capillaries (arrows) are positive, and staining of hematopoietic cells was undetectable. E-cadherin positive epithelial cells (green) at the edge of the crypt were simultaneously visualized using a rabbit polyclonal antibody (Santa Cruz, Santa Cruz, CA), followed by a goat anti-rabbit IgG secondary antibody labelled with alexa (Molecular Probes, Eugene, OR). Sections were imaged at 60X magnification using confocal microscopy. (Fig. 2.B) To isolate pure populations from collagenase dispersed tissues, the epithelial and hematopoietic cell fractions were sequentially removed by negative selection with magnetic beads. The remaining cells were stained with P1H12 and ECs were isolated by positive selection with magnetic beads. (Fig. 2.C) RT-PCR analysis used to assess the purity of the EC preparations. Semiquantitative PCR analysis was performed on cDNA generated either directly from colorectal cancer tissue (unfractionated tumor) or from purified ECs isolated from normal colonic mucosa (normal EC fraction) or colorectal cancer (tumor EC fraction). PCR amplification of the epithelial specific marker cytokeratin 20 (CK20), demonstrated its expression was limited to the unfractionated tumor. Two endothelial specific markers, vWF and VE-cadherin (VE-Cad) showed robust amplification only in the endothelial fractions, validating the purity and enrichment protocol shown in (Fig. 2.B). The ubiquitous housekeeping enzyme GAPDH was observed in all samples.

No signal was detected in the no-template (NT) control. cDNA templates were diluted 1:10, 1:100, 1:1000, 1:4000, and 1:40,000 as indicated by the declining wedge. (Fig. 2.D) The relative expression level of select genes was determined by measuring the tag abundance from several SAGE libraries combined into four groups. The first was composed of ~193,000 tags from the two in vivo-derived EC preparations (Endothelial Cell Fraction) while the second contained a single library of ~57,000 tags containing macrophages and other leukocytes derived from the negative selection (Hematopoietic Fraction). The fourth library contained ~401,000 tags from cultured HUVEC and HMVEC (Endothelial Cells in Culture), and the fourth consisted of ~748,000 tags from 6 colon cancer cell lines in culture (Epithelial Cells). After normalization, the library with the highest tag number for each marker was given a value of 100%, and the corresponding relative expression levels of the remaining 3 libraries was plotted on the ordinate. Note the high level of CD31 present on hematopoietic cells, the likely cause of the impurity of the initial endothelial selection, compared with the selectivity of P1H12.

[49] Fig. 3A- 3E. Expression of Pan-Endothelial Markers (PEMs) is limited to ECs. The endothelial origin of PEMs identified by SAGE was confirmed using a highly sensitive in situ hybridization assay. Localization of novel PEMs to the ECs was demonstrated by examining two representative PEMs, PEM3 (Fig. 3A) and PEM6 (Fig. 3B) in lung cancer and colon cancer, respectively. Hevin expression was readily detected in the ECs of a colon tumor (Fig. 3C) despite its low level of expression in cultured ECs. Expression of VEGFR2 was readily detectable in the ECs of both normal (Fig. 3D) and malignant colon tissue (Fig. 3E).

[50] Fig. 4A-4J. Expression of Tumor Endothelial Markers (TEMs). (Fig. 4A) RT-PCR analysis confirmed the tumor specific expression of selected novel TEMs. Semiquantitative PCR analysis was performed on cDNA generated either from purified epithelial cells as a negative control (Control) or from purified ECs isolated from normal colonic mucosa (Normal ECs) or

colorectal cancer (Tumor ECs) from two different patients. Two endothelial specific markers, vWF and PEM6 showed robust amplification only in the endothelial fractions whereas the ubiquitous housekeeping enzyme GAPDH was observed in all samples. TEM1 (BSC-TEM1), TEM 17 (BSC-TEM7) and TEM22 (BSC-TEM9) were specifically expressed in tumor compared to normal ECs. The cDNA template was diluted 1:10, 1:100, 1:1000, and 1:10,000 as indicated by the declining wedge. (Fig. 4 B- 4J) The endothelial origin of TEMs identified by SAGE was confirmed using in situ hybridization as in Fig 3. Expression of TEM 1 (BSC-TEM1) (Fig. 4 B) and TEM17 (BSC-TEM7) (Fig. 4 C) was demonstrated to be highly specific to the ECs in colorectal cancers; sections were imaged in the absence of a counterstain to show the complete lack of detectable expression in the non-endothelial cells of the tumor. Expression of TEM17 (BSC-TEM7) in ECs was demonstrated in a metastatic liver lesion from a primary colorectal cancer (Fig. 4 D), a lung (Fig. 4 E), breast (Fig. 4 F), pancreatic (Fig. 4 G) and brain cancer (Fig. 4 H), as well as in a sarcoma (Fig. 4 I). TEM 17 (BSC-TEM7) was also localized to vessels during normal physiological angiogenesis of the corpus luteum (Fig. 4 J).

DETAILED DESCRIPTION OF THE INVENTION

[51] We identified 46 human genes that were expressed at significantly higher levels (> 10-fold) in tumor endothelium than in normal endothelium, and 33 genes that were expressed at significantly lower levels in human tumor versus normal endothelium. See Tables 2 and 4, respectively. Most of these genes were either not expressed or expressed at relatively low levels in Endothelial Cells (ECs) maintained in culture. Moreover, we identified 93 genes which are expressed in both normal and tumor human endothelium. Interestingly, the tumor endothelium genes were expressed in all tumors tested, regardless of its tissue or organ source. Most tumor endothelium genes were also expressed in corpus luteum and wounds.

[52] As the work has progressed, we have refined and classified our original 46 tumor endothelial markers. We have named these markers TEMs and renumbered them consecutively by the prevalence of their tags in our SAGE analysis. Originally we had not used a consecutive numbering system. Our non-consecutive numbering system has been renamed as BSC-TEMs. For most of the original 46 SAGE Tags, we now provide full-length nucleic acid and protein sequence. In some cases, the sequences were obtained through the public databases, in others the sequences were obtained by cloning and through the use of gene prediction tools. In some cases, we found SAGE Tags corresponding to genes having different splice varients or with known polymorphisms. For example, in one case the SAGE Tag BSC-TEM3 has been found to hybridize to an alternatively spliced form of the transcript encoding BSC-TEM7. The proteins encoded by the two transcripts are the same; therefore they are cumulatively called TEM7. A highly related sequence was found via homology searches, BSC-TEM7R. This paralog sequence is now called TEM3. See Table 2, which follows, showing tumor endothelial markers by order of prevalence (except for TEM 3). Column 1 indicates the prevalence number. Column 2 indicates the original nomenclature. Column 3 indicates the short tags. Column 4 indicates the long tags. Column 5 indicates the accession number in GenBank. Column 6 indicates the sequence identifiers for the short tag, the long tag, the full nucleic acid, and the protein. Column 7 provides a functional description, which is expanded below in the text.

TEM1	BSC-TEM1	GGGGCTGCCCA	GGGGCTGCCCAGCTGA	NM020404	SEQ ID NO: 94, 309, 195, 196	tumor endothelial marker 1 precursor
TEM 2	BSC-TEM2	GATCTCCGTGT			SEQ ID NO: 95, 197.198	sapiens tumor endothelial marker 2 (BSC-TEM2) mRNA/mouse Ras, dexamethasone-induced 1 (RASD1), mRNA
TEM 3	BSC-TEM7R				SEQ ID NO:199, 200, 359	human ortholog of mouse paralog of mouse TEM-7
TEM 4		CTTTCTTTGAG	CTTTCTTTGAGTTTTAA	AB034203	SEQ ID NO:97, 311, 201, 202	Homo sapiens dickkopf-3 (DKK-3) mRNA,
TEM 5	BSC-TEM4	TATTAACTCTC	TATTAACTCTCTTTGGA		SEQ ID NO:98, 312, 203, 204	Tumor endothelial marker 4
TEM 6		CAGGAGACCCC	CAGGAGACCCCAGGCCC	X57766	SEQ ID NO:99, 314, 205, 206	Human stromelysin-3 mRNA.
TEM 7		GGAAATGTCAA	GGAAATGTCAGCAAGTA	BC002576	SEQ ID NO:100, 315.207, 208	matrix metalloproteinase 2 (gelatinase A, 72kD gelatinase, 72kD type IV collagenase)

TEM 8		CCTGGTTCAGT			SEQ ID NO:101, 316, 209, 210	HeyL transcription factor
TEM 9	BSC-TEM5	TTTTTAAGAAC	TTTTTAAGAACTCGGGT		SEQ ID NO:102, 317, 211, 212	
TEM 10		TTTGGTTTTCC	TTTGGTTTTCCAAAAGA	J03464, M18057, X02488	SEQ ID NO:103, 319, 213, 214	Human collagen alpha-2 type I mRNA, complete cds, clone pHCOL2A1.
TEM 11		ATTTTGTATGA	ATTTTGTATGATTTTTA	NM_002508	SEQ ID NO:104, 321, 215, 216	nidogen/entactin
TEM 12		ACTTTAGATGG	ACTTTAGATGGGAAGCC	X52022	SEQ ID NO:105, 322, 217, 218	H.sapiens RNA for type VI collagen alpha3 chain.
TEM 13		GAGTGAGACCC	GAGTGAGACCCAGGAGC	M11749	SEQ ID NO:106, 324, 219, 220	Human Thy-1 glycoprotein gene, complete cds.
TEM 14		GTACACACACC	GTACACACACCCCCACC		SEQ ID NO:107, 325, 221, 223	Cystatin SN

TEM 14		GTACACACACC	GTACACACACCCCCACC	X54667	SEQ ID NO:107, 325, 222, 224	H.sapiens mRNA for cystatin S.
TEM 15		CCACAGGGGAT	CCACAGGGGATTCTCCT	NM_000090	SEQ ID NO:108, 327, 225, 226	Human mRNA 3' region for pro-alpha1(III) collagen.
TEM 16	BSC-TEM6	TTAAAAGTCAC	TTAAAAGTCACTGTGCA		SEQ ID NO:109, 328, 227, 228	
TEM 17	BSC-TEM7	ACAGACTGTTA	ACAGACTGTTAGCCAAG	AF279144	SEQ ID NO:110, 329, 229, 230	Human Tumor endothelial marker 7
TEM 18		CCACTGCAACC			SEQ ID NO:111	
TEM 19	BSC-TEM8	CTATAGGAGAC			SEQ ID NO:112, 330, 231, 232	
TEM 20		GTTCCACAGAA		NM_000089	SEQ ID NO:113, 233, 234	collagen, type I, alpha 2 (COL1A2

TEM 21		TACCACCTCCC	TACCACCTCCCTTTCCT		SEQ ID NO:114, 331, 235, 236	Homo sapiens mRNA; cDNA DKFZp762B245 (from clone DKFZp762B245);
TEM 22	BSC-TEM9	GCCCTTTCTCT	GCCCTTTCTCTGTAGTT	NM_006039	SEQ ID NO:115, 334, 237, 238	endocytic receptor (macrophage mannose receptor family) (KIAA0709),
TEM 23		TTAAATAGCAC	TTAAATAGCACCTTTAG		SEQ ID NO:116, 335	no match
TEM 24		AGACATACTGA	AGACATACTGACAGAAT	NM_022648	SEQ ID NO:117, 336, 239, 240	Homo sapiens mRNA; cDNA DKFZp434G162 (from clone DKFZp434G162);
TEM 25		TCCCCCAGGAG	TCCCCCAGGAGCCACCG	L35279, NM_006129	SEQ ID NO:118, 338, 241, 242	Homo sapiens (clone KT2) bone morphogenetic protein-1 (BMP-1) mRNA
TEM 26		AGCCCAAAGTG			SEQ ID NO:119	No Match
TEM 27		ACTACCATAAC		NM_003062	SEQ ID NO:120, 243.244	Homo sapiens mRNA for MEGF5, partial cds.
TEM 28		TACAAATCGTT	TACAAATCGTTGTCAAA	NM_014859	SEQ ID NO:121, 339, 245, 246	Homo sapiens mRNA for KIAA0672 protein, complete cds.

TEM 29		TTGGGTGAA AA			SEQ ID NO:122, 247, 248	ESTs (2 unigene clusters)
TEM 30		CATTATCCAA A	CATTATCCAAAAACA AT	THC534029, X68742, AI262158, AI88747, AI394565, AA679721	SEQ ID NO:123, 340, 249, 250	integrin, alpha 1
TEM 31		AGAAACCAC GG	AGAAACCACGGAAA TGG	NM_001845	SEQ ID NO:124, 341, 251, 252	hypothetical protein KIAA1164
TEM 32		ACCAAAACC AC			SEQ ID NO:125	no match
TEM 33		TGAAATAAAC		NM_000255	SEQ ID NO:126, 253, 254	methylmalonyl Coenzyme A mutase
TEM 34		TTTGGTTTCC			SEQ ID NO:127	no match
TEM 35		GTGGAGACG GA	GTGGAGACGGACTC TGT	ESTAI186535	SEQ ID NO:128, 345, 255, 358	est

TEM 36		TTTGTGTTGTA	TTTGTGTTGTATATTTA	NM_004370	SEQ ID NO:129, 346, 256, 257	est
TEM 37		TTATGTTTAAT	TTATGTTTAATAGTTGA	NM_002345	SEQ ID NO:130, 347, 258, 259	Human lumican mRNA, complete cds.
TEM 38		TGGAAATGAC	TGGAAATGACCCAAAAA	NM_000088	SEQ ID NO:131, 348, 260, 261	collagen type1 alpha1
TEM 39		TGCCACACAGT	TGCCACACAGTGACTTG	NM_003239	SEQ ID NO:132, 350, 262, 263	Human transforming growth factor-beta 3 (TGF-beta3) mRNA, complete
TEM 40		GATGAGGAGAC	GATGAGGAGACTGGCAA		SEQ ID NO:133, 351, 264, 265	collagen, type I, alpha 2
TEM 41		ATCAAAGGTTT	ATCAAAGGTTTGATTTA		SEQ ID NO:134, 352, 266, 267	est
TEM 42		AGTCACTAGT	AGTCACATAGTACATAA	NM_025226	SEQ ID NO: 135, 353, 268, 269	ESTs

TEM 43		TTCGGTTGG TC	TTCGGTTGGTCAAA GAT		SEQ ID NO:136, 354	No match
TEM 44		CCCCACACG GG	CCCCACACGGGCAA GCA	NM_01835 4v	SEQ ID NO: 137, 355, 270, 271	Homo sapiens cDNA FLJ11190 fis, clone PLACE1007583.
TEM 45		GGCTTGCCT TT	GGCTTGCCTTTTTGT AT	NM_00036 6	SEQ ID NO:138, 356, 272, 273	est
TEM 46		ATCCCTTCCC G	ATCCCTTCCCGCCA CAC	NM_00268 8	SEQ ID NO:139, 357, 274, 275	Homo sapiens mRNA for peanut-like protein 1, PNUTL1 (hCDCrel-1).

[53] The studies described below provide the first definitive molecular characterization of ECs in an unbiased and general manner. They lead to several important conclusions that have direct bearing on long-standing hypotheses about angiogenesis. First, it is clear that normal and tumor endothelium are highly related, sharing many endothelial cell specific markers. Second, it is equally clear that the endothelium derived from tumors is qualitatively different from that derived from normal tissues of the same type and is also different from primary endothelial cultures. Third, these genes are characteristically expressed in tumors derived from several different tissue types, documenting that tumor endothelium, in general, is different from normal endothelium. Fourth, the genes expressed differentially in tumor endothelium are also expressed during other angiogenic processes such as corpus luteum formation and wound healing. It is therefore more appropriate to regard the formation of new vessels in tumors as "neoangiogenesis" rather than "tumor angiogenesis" *per se*. This distinction is important from a variety of perspectives, and is consistent with the idea that tumors recruit vasculature using much of, or basically the same signals elaborated during other physiologic or pathological processes. That tumors represent "unhealed wounds" is one of the oldest ideas in cancer biology.

[54] The nature and precise biological function of many of the Tumor Endothelial Markers (TEMs) identified here are unknown. Of the previously characterized genes shown in Table 2, it is intriguing that several encode proteins involved in extracellular matrix formation or remodelling (TEM 6, TEM 6, TEM 10, TEM 7, TEM 11, TEM 12, TEM 14, TEM 20, TEM 24, TEM 25, TEM 27, TEM 37, TEM 38, and TEM 40,) Deposition of extracellular matrix is likely critical to the growth of new vessels. Finally, it is perhaps not surprising that so many of the endothelial-specific transcripts identified here, whether expressed only in neovasculature or in endothelium in general, have not been previously characterized, and some are not even represented in EST databases. In part, this may be due to the fact that the EST databases are heavily biased toward certain tissues, but moreover, may be due to the fact that even in highly vascularized tissues endothelial cells are still a

relatively small proportion of the population. Thus, the sensitivity of the SAGE method is a particularly appropriate tool.

[55] Sequence and literature study has permitted the following identifications to be made among the family of TEM proteins. TEM proteins have been identified which contain transmembrane regions. These include TEM 1, TEM 3, TEM 9, TEM 13, TEM 17, TEM 19, TEM 22, TEM 30, and TEM 44. TEM proteins have been identified which are secreted proteins, including TEM 4, TEM 6, TEM 7, TEM 10, TEM 12, TEM 14, TEM 20, TEM 25, TEM 27, TEM 31, TEM 36, TEM 37, TEM 38, and TEM 39. HeyL (TEM 8) is a transcription factor which may be involved in regulating TEMs as one or more groups. The protein corresponding to the tag for TEM44 was found in the public databases, but no biological function has yet been ascribed to it.

[56] TEM 1 has been named endosialin in the literature. It has a signal sequence at amino acids 1-17 and a transmembrare domain at amino acids 686-708. Thus it is a cell surface protein. Its extracellular domain is at resiudes 1-685. Endosialin may be involved in endocytosis. The mouse ortholog is predicte d to have a signal peptide at residues 1-21.

[57] TEM 2 is a dexamethasone induced, ras related protein homolog of 266 amino acids. It has neither a signal sequence nor a transmembrane domain. Thus it is neither a cell surface nor a secreted protein. TEM 2 plays a role in signal transduction. It regulates alterations in cell morphology, proliferation, and cell-extracellular matrix interactions.

[58] TEM 3 (originally termed TEM 7R) has both a signal sequence (at residues 1-24 or 1-30) and a transmembrane domain (at residues 456 – 477). Thus it is a cell surface protein. The portion of the protein which is extracelular is at amino acids 1- 455. TEM 3 has domains with homology to integrins, plexin, and adhesion molecules. TEM 3 may regulate GTPases that control signal transduction pathways linking plasma membrane receptors to

the actin cytoskeleton. In the mouse ortholog, the signal peptide is predicted to be residues 1-30.

[59] TEM 4 is also known as DKK –3. It has a signal sequence (residues1-16), suggesting that is a secreted protein. TEM 4 regulates *wnt* signaling, and it may be involved in vasculogenesis and *wnt*-dependent signaling for endothelial growth. TEM 4 is an inhibitor of Wnt oncogene and such inhibition can be determined by assay. Tsuji et al., Biochem.Biophys.Res.Comm. 268:20-4, 2000.

[60] TEM 5 appears to be neither secreted nor a cell surface protein. TEM 5 appears to be a component of a G protein - GTPase signaling pathway.

[61] TEM 6 is also known as stromelysin - 3 /Matrix metalloproteinase 11 (MMP -11). It has a signal sequence at residues 1-31, but no transmembrane domain. It has an alternative signal peptide splice site at residues 108-109. Thus it appears to be a secreted protein. TEM 6 belongs to the zinc metaloprotease family, also known as the matrixin subfamily. TEM 6 is expressed in most invasive carcinomas. Alpha 1 - protease inhibitor is a natural substrate of MMP 11. TEM 6 degrades extracelllular matrix proteins such as collagen and is involved in extracellular matrix remodeling and cell migration. Stromelysin can be assayed using a casein-resorufin substrate, for example. See Tortorella and Arner, Inflammation Research 46 Supp. 2:S122-3, 1997.

[62] TEM 7 is a protein of many names, also being known as matrix metalloproeinase 2, gelatinase A, and 72KD type IV collagenase. TEM 7 has a signal sequence at residues 1- 26 and is a secreted protein. Like TEM 6, TEM 7 belongs to the matrixin subfamily (zinc metalloproteinases). TEM 7 cleaves gelatin type I, collagen type I, IV, V VII and X.. TEM 7 associates with integrin on the surface of endothelial cells and promotes vascular invasion. TEM 7 is involved in tissue remodeling. TEM 7 can be assayed using zymography or quenched fluorescent substrate hydrolysis, for example.

Garbett, et al., Molecular Pathology 53:99-106, 2000. A fluorogenic matrix metalloproteinase substrae assay can also be used which employs methoxycoumarin continaing septapeptide analog of the alpha2(I) collagen cleavage site. See Bhide et al., J. Periodontology 71:690-700, 2000.

[63] TEM 8 is HEYL protein . It has neither a signal sequence nor a transmembrane domain. It is related to the hairy/Enhancer of split genes. TEM 8 is likely a nuclear protein, having a role as a transcription factor. TEM 8 belongs to a new class of Notch signal tranducers and plays a key role in various developmental processes, such as vascular development, somatogenesis and neurogenesis. SNP's at residues 615 and 2201 have Cytosine bases. Notch 3 mutations underlie the CADASIL vascular disorder. See *Mech Dev* 2000 Nov; 98 (1-2):175

[64] TEM 9 is a G- protein coupled receptor homolog, having both a signal sequence at residues 1-26 and 7 transmembrane domains. Thus it is a cell surface protein. Its extracellular region resides in amino acids 1-769. Its transmembrane domains are at residues 817-829 (TM2 and TM3), residues 899-929 (TM4 and TM5), and residues 1034-1040 (TM6 and TM7). TEM 9 acts as a G-protein coupled receptor with extracellular domains characteristic of cell adhesion proteins. One of its splice variants may function as a soluble receptor. TEM 9 may regulate cell polarity and cell migration. It may be involved in exocytosis based on latrophilin function. The mouse ortholog has a predicted signal peptide at residues 1-29.

[65] TEM 10 is collagen type I, alpha2 (COL1A2), which has a signal sequence at residues 1-22. It is an extracellular matrix (ECM) protein which is secreted subsequent to synthesis. TEM 10 interacts with a number of proteins including other ECM proteins, certain growth factors, and matrix metalloproteases. TEM 10 is required for the induction of endothelial tube formation and is involved in tissue remodeling. A variant at nucleotide 3233 which substitutes an A, is associated with osteogenesis imperfecta type IV. A variant at nucleotide 4321 substituting an A retains a wild type phenotype.

Nucleotide 715 is a site of a polymorphism. Nucleotides 695-748 are deleted in Ehlers-Danos syndrome. Other mutations are associated with idiopathic osteoporosis, and atypical Marfan syndrome. Variants are known at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784 (G,C), 2017(T,G), 2172(C,A), 2284(T,C), 2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2974(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T). PolyA sites are located at nucleotides 4450, 4550, 4885, and 5082. PolyA signals are located at 4420-4424, 4515-4520, 4529-4534, 4866-4871, 5032-5037, 5053-5058. TEM 10, 20, and 40 derive from the same gene but are different isoforms having different lengths.

[66] TEM 11 is Nidogen /Entactin. It is a secreted protein which has a signal sequence at residues 1-28. TEM 11 is an extracellular matrix protein which is a component of a basement membrane. TEM 11 binds to laminin and collagen IV and other extracellular matrix proteins. TEM 11 regulates capillary formation and is involved in tissue remodelling. Variations have been observed at nucleotides 4265(T,C), 4267(G,C,T), and 4738(T,G). Nidogen can be assayed by its effect on the morphology of astrocytes. See Grimpe et al., GLIA 28:138-49, 1999.

[67] TEM 12 is the alpha 3 chain of collagen type VI. It has a signal sequence at residues 1-25. A secreted protein, TEM 12 is an extrallcellular matrix protein. TEM 12 has a splice variant. TEM 12 is a major constituent of vascular subendothelium and is involved in tissue remodeling. It regulates platelet activation and aggregation. Alternatively spliced domains are located at nucleotides 347-964, 965-1567, 2153-3752, and 4541-5041.

[68] TEM 13 is also known as Thy -1 glycoprotein. It has both a signal sequence (at residues 1-19) and a transmembrane domain (at residues 143-159). Residues 131-161 are removed in a matured form of the protein. The extracellular region of the protein is resudes 1- 142 or residues 1-130. TEM

13 has a glycosyl phosphatidylinositol (GPI) anchor at residue 130 anchoring it to the membrane. TEM 13 is detectale in its soluble form in human serum. TEM 13 is reported to be a marker for activated endothelial cells (a marker of adult but not embryonic angiogenesis). TEM 13 on vascular endothelial cells may function as a possible vascular permeability modulator. Antibody to Thy-1 is a mitogenic signal for the CD4+CD45+ and CD8+CD45+ cells, but fails to induce proliferation in the CD45- T cells. Pingel et al., International Immunology 6:169-78, 1994. Thy-1 can be assayed as an inhibitor of such signal.

[69] TEM 14 is also known as cystatin S. It is a secreted protein with a signal sequence at residues 1-20 and an extracelllular region at residues 1-141. It is a cysteine protease inhibitor. TEM 14 may regulate cysteine protease function involved in angiogenesis and tissue remodeling. TEM14 is an inhibitor of the activity of papain and such inhibition can be assayed. Hiltke et al., J. Dental Research 78:1401-9, 1999.

[70] TEM 15 is collagen type III, alpha 1 (COL3A1). It has a signal sequence (residues 1-23) and is secreted. Type III collagen binds to von Willebrand factor. It is involved in cell-cell adhesion, proliferation, and migration activities. Variants at nucleotides 2104(C,A), 2194(G,A), 2346(C,T), 2740(C,T), 3157(T), 3468(G), 3652(T), 3666(C), 3693(C), 3755(G), 3756(T), 3824(C), 4546(A, G), 4661(G), 4591(C,T), 4665(C), 5292(C), 5293(C), and 5451 (A) have been observed.

[71] TEM 16 is a tensin homolog which is apparently an intracellular protein. It may have splice variants or isoforms. One form with 1704 amino acids has a region at the N-terminal domain which is similar to a tumor suppressor protein, phosphatase and tensin homolog (PTEN). Tensin is a focal adhesion molecule that binds to actins and phosphorylated proteins. It is involved in cell migration linking signal tranduction pathways to the cytoskeleton. PTEN regulates tumor induced angiogenesis.

[72] TEM 17 (BSC-TEM 7) has a signal sequence which includes residues 1-18 and a transmembrane domain at residues 427-445. It is a cell surface marker with an extracellular region comprising residues 1-426. It has homologs in both mouse and *C. elegans*. Residues 137-244 share weak homology with nidogen; residues 280-344 share homology to PSI domains found in plexin, semaphorins and integrin beta subunits. Variants have been observed at nucleotides 1893(A,G), 1950(C,G), 2042(A,G), and 2220(G,A). In mouse TEM 17 the signal sequence includes residues 1-19.

[73] TEM 19 was originally reported to be tumor endothelial marker 8, *i.e.*, BSC-TEM 8. It has a signal sequence at residues 1-27 and a transmembrane domain at residues 322-343. It is a cell surface protein having an extracellular region at residues 1-321.TEM 19 has a von Willebrand Factor (vWF) A domain at residues 44-216; a domain at residues 34-253 which is found in leukointegrin alpha D chain; and a domain at residues 408-560 found in PRAM-1 or adaptor molecule –1 of the vinculin family. TEM 19's function is adhesion related. vonWillibrand Factor domains are typically involved in a variety of functions including vascular processes. TEM 19 may play a role in the migration of vascular endothelial cells. The mouse ortholog has a predicted signal peptide at residues 1-27.

[74] TEM 20 is collagen type I, alpha 2 (COL1A2). It has a signal sequence at residues 1-22 and is a secreted extracellular matrix protein. TEM 20 induces endothelial tube formation *in vitro* and is involved in tissue remodeling. Variants have been observed at nucleotides 226(T,C), 314(A,C), 385(T,C), 868 (G,A), 907(C,T), 965(A,G), 970(T,A), 1784(G,C), 2017(T,G), 2172(C,A), 2284(T,C), 2308(T,C), 2323(T,G), 2344(T,G), 2604(G,A), 2794(A,T), 2903(A,G), 2995(C,T), 3274(C,T), 3581(A,C), 3991(A,C), 4201(G,T), 4434(C,T), 4551(A,C), 4606(C,A), 4895-4901(--, GGACAAC), 4947(T,C), 4978(C,T), 4982(G,T), 5051(G,T).

[75] TEM 21 is a Formin – like protein homolog which is an intracellular protein. Formin related proteins interact with Rho family small GTPases,

profilin, and other actin associated proteins. Formin-binding proteins bind to FH1 domains with their WW domains. TEM 21 has a proline rich FH1 domain at residues 221-449. Formin related proteins play crucial roles in morphogenesis, cell polarity , cytokinesis and reorganization of the actin cytoskeleton. They may also regulate apoptosis, cell adhesion and migration.

[76] TEM 22 is an endocytic receptor in the macrophage mannose receptor family. It has both a signal sequence at residues 1-30 and a transmembrane domain at residues 1415-1435, and resides on the cell surface. Its extracellular domain is amino acids 1- 1414. TEM 22 may be present as a soluble (secreted) form and act as an inhibitor. It may bind secreted phopholipase A2 (sPLA2) and mediate biological responses elicited by sPLA2. TEM 22 may have endocytic properties for sPLA2 and mediate endocytosis for endothelial related proteins. It may promote cell adhesion and be involved in cell-cell communication. Variations have been observed at nucleotide 5389 (A, G). TEM 22 mediates uptake of micro-organisms and host-derived glycoproteins. Groger et al., J. Immunology 165:5428-34, 2000.

[77] TEM 24 is tensin, an intracellular protein. It is a focal adhesion molecule that binds to actin filaments and interacts with phosphotyrosine containing proteins. It may mediate kinase signaling activities and regulate cellular transformation. Variations have been observed at nucleotides 2502 (A, G), 2622(A, G), 6027(A, G). TEM24 binds to actin filaments and interacts with phosphotyrosine-containing proteins. Chen et al., Biochem. J. 351 Pt2:403-11, 2000. TEM24 also binds to phosphoinositide3-kinase. Auger et al., J. Bio. Chem. 271:23452-7, 1996 TEM 24 also binds to nuclear protein p130. Lo et al., Bioessays 16:817-23, 1994.

[78] TEM 25 is Bone morphogenic protein 1 (BMP-1) which has a signal sequence at residues 1-22. It is a secreted protein. There are at least 6 isoforms of BMP-1 as well as splice variants which add carboxy terminal CUB domains and an additional EGF domain. TEM 25 is a metalloprotease enzyme. It cleaves the C-terminal propeptide of collagen type I, II and III and

laminin 5 gamma 2 , proteins that are important for vascular processes. It is involved in cartilage formation. Variations have been observed at nucleotides 3106(C,T), 3248(G,A), 3369(G,A). TEM 25 cleave probiglycan at a single site, removing the propeptide and producing a biglycan molecule with an NH(2) terminus identical to that of the mature form found in tissues. Sctt et al., J. Biol. Chem. 275:30504-11, 2000. Laminin alpha 3 and gamma2 short chains are substraates of TEM 25. Amano et al., J. Biol. Chem. 275:22728-35, 2000.

[79] TEM 27 is known as Slit homolog 3, a secreted protein with a signal sequence at residues 1-27. TEM 27 is a secreted guide protein involved in migration, repulsion and patterning. It interacts with "round about" receptors (Robo receptors). TEM 27 may interact with extracellular matrix (ECM) proteins and is involved in cell adhesion. Variations have been observed at nucleotides 4772 (C,T)

[80] TEM 28 is similar to mouse nadrin (neuron specific GTPase activiating protein). TEM 28 is an intracellular protein with a RhoGAP domain. The RhoGAP domain activates RhoA, Rac1, and Cdc42 GTPases. It is involved in the reorganization of actin filaments and enhancing exocytosis. It may also be involved in cell signalling. Variations have been observed at nucleotide 3969 (A,C),

[81] TEM 29 is protein tyrosine phosphatase type IVA, member 3, isoform 1, an intracellular protein. It has alternate splice variants. TEM 29 belongs to a small class of prenylated protein tyrosine phosphatases (PTPs). It may be membrane associated by prenylation. PTPs are cell signaling molecules and play regulatory roles in a variety of cellular processes and promote cell proliferation. PTP PRL-3 regulates angiotensin –II induced signaling events.

[82] TEM 30 is integrin alpha 1, a cell surface protein having both a signal sequence (residues 1-28) and a transmembrane domain (residues 1142- 1164). Its extracellular region includes amino acids 1-1141. TEM 30 is a receptor for

laminin and collagen. It mediates a variety of adhesive interactions. TEM 30 is abundantly expressed on microvascular endothelial cells. It stimulates endothelial cell proliferation and vascularization. TEM 30 may regulate angiostatin production. Variations have been observed at nucleotide 418 (C,T). TEM 30 activates the Ras/Shc/mitogen-activated protein kinase pathway promoting fibroblast cell proliferation. It also acts to inhibit collagen and metalloproteinase synthesis. Pozzi et al., Proc. Nat. Acad. Sci. USA 97:2202-7, 2000,

[83] TEM 31 is Collagen IV alpha 1 (COL4A1) a secreted protein with a at residues 1-27. TEM 31 is a component of the basement membrane. It binds to alpha3 beta 1integrin and promotes integrin mediated cell adhesion. Non-collagenous domains of type IV subunits are involved in tumoral angiogenesis. TEM 31 is involved in tissue remodeling. Variations have been observed at nucleotide 4470 (C,T)

[84] TEM 33 is methylmalonyl Co-A Mutase a protein which is localized in the mitochondrial matrix. It degrades several amino acids, odd-numbered-acid fatty acids, and cholesterol to the tricarboylic acid cycle. A defect in TEM 33 causes a fatal disorder in organic acid metabolism termed methylmalonic acidurea. Variations have been observed at nucleotides 1531(G,A), 1671(G,A), 2028(T,C), 2087(G,A), 2359(A,G), 2437(C,A), 2643(G,C), 2702(G,C). TEM 33 converts L-methylmalonyl CoA to succinyl CoA. This reaction can be assayed as is known in the art. See, e.g., Clin. Chem. 41(8 Pt I):1164-70, 1995.

[85] TEM 36 is collagen type XII, alpha1 (COL12A1) , an extracellular matrix protein having a signal sequence at residues 1-23 or 24. TEM 36 has von Willebrand Factor (vWF) type A domains, Fibronectin type III domains, and thrombospondin N-terminal like domain. TEM 36 is expressed in response to stress environment. TEM 36 may organize extracellular matrix architecture and be involved in matrix remodeling. There are two isoforms of the protein, a long form and a short form. The short form is missing amino acids 25-1188,

and therefore nucleotides 73 to 3564. Both forms share the signal sequence and are therefore both secreted.

[86] TEM 37 is lumican, an extracellular matrix sulfated proteoglycan having a signal sequence at residues 1-18. Lumican interacts with proteins that are involved in matrix assembly such as collagen type I and type VI; it is involved in cell proliferation and tissue morphogenesis. Lumican plays an important role in the regulation of collagen fiber assembly. Variations have been observed at nucleotides 1021(G,T), 1035(A,G), 1209(A,G), 1259(A,C), 1418(C,A), 1519(T,A). TEM 37 is a binding partner of TGF-β. See FASEB J. 15:559-61, 2000. One assay that can be used to determine TEM 37 activity is a collagen fibril formation/sedimentation assay. Svensson et al., FEBS Letters 470:178-82, 2000.

[87] TEM 38 is collagen type I, alpha 1 (COL1A1), an extracellular matrix protein having a signal sequence at residues 1-22. Type I collagen promotes endothelial cell migration and vascularization and induces tube formation and is involved in tissue remodelling. Telopeptide derivative is used as a marker for malignancy and invasion for certain cancer types. Variations have been observed at nucleotides 296(T,G), 1810(G,A), 1890(G,A), 2204(T,A), 3175(G,C), 3578(C,T), 4298(C,T), 4394(A,T), 4410(A,C), 4415(C.A), 4419 (A,T), 4528(C,A), 4572(G,T), 4602(T,C), 5529(T,C), 5670(C,T), 5985(C,T), 6012(C,T).

[88] TEM 39 is transforming growth factor β –3 (TGF-beta3). It has a signal sequence at residues 1-23. It is a secreted protein. TEM 39 regulates cell growth and differentiation. TGF-beta isoforms play a major role in vascular repair processes and remodeling. Variations have been observed at nucleotide 2020(G,T).

[89] TEM 41 is similar to Olfactomedin like protein. It appears to be an intracellular protein, having no obvious predicted signal sequence. Olfactomedin is the major glycoprotein of the extracellular mucous matrix of

olfactory neuroepithelium. TEM 41 shares homology with latrophilin (extracellular regions) which has cell-adhesive type domains. TEM 41 may be involved in adhesive function.

[90] **TEM 42 is MSTP032 protein, a cell surface protein having a trasmembrane domain at residues 42-61. Its function is unknown and it shares little homology with other proteins. Variations have been observed at nucleotides 418(A,T), 724(C,A).**

[91] TEM 44 is a hypothetical protein FLJ11190 (NM_018354) which has two predicted transmembrane domains at residues 121-143 and 176 –1 97. Residues 144-175 may form an extracellular region. TEM 44's function is not known and shares no homology to other known proteins.

[92] TEM 45 is tropomyosin 1 (alpha), a protein which is intracellular. It forms dimers with a beta subunit. It influences actin function. TEM 45 may be involved in endothelial cell cytoskeletal rearrangement. Variations have been observed at nucleotides 509(A,C), 621(A,C), 635(T,G), 642(C,G), 1059(G,T).

[93] TEM 46 is peanut-like 1 protein/septin 5, which belongs to the septin family. Proteins in the septin family bind to GTP and phosphatidylinositol 4,5-bisphosphate. They are involved in the signal tranduction cascades controlling cytokinesis and cell division.

[94] NEM 4 is a member of the small inducible cytokine subfamily A (cys-cys), member 14 (SCYA14). NEM4 is a secreted protein characterized by two adjacent cysteine residues. One isoform lacks internal 16 amino acids compared to isoform 2.

[95] NEM 22 shares homology with guanylate kinase-interacting protein 1Maguin-1. It is a membrane associated protein.

[96] NEM 23 is human signaling lymphocytic acitavation molecule (SLAM). It has a signal sequence at residues 1-20. The extracellular domain may reside at residues 21-237. There is a secreted isoform of the protein.

[97] NEM33 is netrin 4. It induces neurite outgrowth and promotes vascular development. At higher concentration, neurite outgrowth is inhibited.

[98] ECs represent only a minor fraction of the total cells within normal or tumor tissues, and only those EC transcripts expressed at the highest levels would be expected to be represented in libraries constructed from unfractionated tissues. The genes described in the current study should therefore provide a valuable resource for basic and clinical studies of human angiogenesis in the future. Genes which have been identified as tumor endothelial markers (TEMs) correspond to tags shown in SEQ ID NOS: 94-139, 173-176, 180-186. Genes which have been identified as normal endothelial markers (NEMs) correspond to tags shown in SEQ ID NOS: 140-172. Genes which have been identified as pan-endothelial markers (PEMs) *i.e.,* expressed in both tumor and normal endothelial cells correspond to tags shown in SEQ ID NOS: 1-93. Genes which have been previously identified as being expressed predominantly in the endothelium correspond to PEM tags shown in SEQ ID NOS: 1-6, 8, 10-15. Markers in each class can be used interchangeably for some purposes.

[99] Isolated and purified nucleic acids, according to the present invention are those which are not linked to those genes to which they are linked in the human genome. Moreover, they are not present in a mixture such as a library containing a multitude of distinct sequences from distinct genes. They may be, however, linked to other genes such as vector sequences or sequences of other genes to which they are not naturally adjacent. Tags disclosed herein, because of the way that they were made, represent sequences which are 3' of the 3' most restriction enzyme recognition site for the tagging enzyme used to generate the SAGE tags. In this case, the tags are 3' of the most 3' most NlaIII site in the cDNA molecules corresponding to mRNA. Nucleic acids corresponding to tags may be RNA, cDNA, or genomic DNA, for example.

Such corresponding nucleic acids can be determined by comparison to sequence databases to determine sequence identities. Sequence comparisons can be done using any available technique, such as BLAST, available from the National Library of Medicine, National Center for Biotechnology Information. Tags can also be used as hybridization probes to libraries of genomic or cDNA to identify the genes from which they derive. Thus, using sequence comparisons or cloning, or combinations of these methods, one skilled in the art can obtain full-length nucleic acid sequences. Genes corresponding to tags will contain the sequence of the tag at the 3' end of the coding sequence or of the 3' untranslated region (UTR), 3' of the 3' most recognition site in the cDNA for the restriction endonuclease which was used to make the tags. The nucleic acids may represent either the sense or the anti-sense strand. Nucleic acids and proteins althought disclosed herein with sequence particularity, may be derived from a single individual. Allelic variants which occur in the population of humans are including within the scope of such nucleic acids and proteins. Those of skill in the art are well able to identify allelic variants as being the same gene or protein Given a nucleic acid, one of ordinary skill in the art can readily determine an open reading frame present, and consequently the sequence of a polypeptide encoded by the open reading frame and, using techniques well known in the art, express such protein in a suitable host. Proteins comprising such polypeptides can be the naturally occurring proteins, fusion proteins comprising exogenous sequences from other genes from humans or other species, epitope tagged polypeptides, etc. Isolated and purified proteins are not in a cell, and are separated from the normal cellular constituents, such as nucleic acids, lipids, etc. Typically the protein is purified to such an extent that it comprises the predominant species of protein in the composition, such as greater than 50, 60 70, 80, 90, or even 95% of the proteins present.

[100] Using the proteins according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an

antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[101] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p. 1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods 231* 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D, Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal

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761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al., U.S. 6,1075,181.

[102] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[103] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample. Antibodies can also be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis Factor (TNF); photosensitizers, for

use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m (^{99m}Tc), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (naja naja atra), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*, antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

[104] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.

[105] Characterization of extracellular regions for the cell surface and secreted proteins from the protein sequence is based on the prediction of signal sequence, transmembrane domains and functional domains. Antibodies are preferably specifically immunoreactive with membrane associated proteins, particularly to extracellular domains of such proteins or to secreted proteins. Such targets are readily accessible to antibodies, which typically do not have access to the interior of cells or nuclei. However, in some applications, antibodies directed to intracellular proteins may be useful as well. Moreover, for diagnostic purposes, an intracellular protein may be an equally good target since cell lysates may be used rather than a whole cell assay.

[106] Computer programs can be used to identify extracellular domains of proteins whose sequences are known. Such programs include SMART software (Schultz et al., Proc. Natl. Acad. Sci. USA *95:* 5857-5864, 1998) and Pfam software (Bateman et al., Nucleic acids Res. *28: 263-266, 2000)* as well as PSORTII. Typically such programs identify transmembrane domains; the extracellular domains are identified as immediately adjacent to the transmembrane domains. Prediction of extracellular regions and the signal cleavage sites are only approximate. It may have a margin of error + or – 5 residues. Signal sequence can be predicted using three different methods (Nielsen et al, *Protein Engineering* 10: 1-6 ,1997, Jagla et. al, Bioinformatics 16: 245-250 , 2000, Nakai, K and Horton, P. Trends in Biochem. Sci. 24:34-35, 1999) for greater accuracy. Similarly transmembrane (TM) domains can be identified by multiple prediction methods. (Pasquier, et. al, Protein Eng. 12:381-385, 1999, Sonnhammer et al., In Proc. of Sixth Int. Conf. on Intelligent Systems for Molecular Biology, p. 175-182 , Ed J. Glasgow, T. Littlejohn, F. Major, R. Lathrop, D. Sankoff, and C. Sensen Menlo Park, CA: AAAI Press, 1998 , Klein, et.al, Biochim. Biophys. Acta, 815:468, 1985, Nakai and Kanehisa Genomics, 14: 897-911 , 1992). In ambiguous cases, locations of functional domains in well characterized proteins are used as a guide to assign a cellular localization.

[107] Putative functions or functional domains of novel proteins can be inferred from homologous regions in the database identified by BLAST searches (Altschul et. al. Nucleic Acid Res. 25: 3389-3402, 1997) and/or from a conserved domain database such as Pfam (Bateman et.al, Nucleic Acids Res. 27:260-262 1999) BLOCKS (Henikoff, et. al, Nucl. Acids Res. 28:228-230, 2000) and SMART (Ponting, et. al, Nucleic Acid Res. 27,229-232, 1999). Extracellular domains include regions adjacent to a transmembrane domain in a single transmembrane domain protein (out–in or type I class). For multiple transmembrane domains proteins, the extracellular domain also includes those regions between two adjacent transmembrane domains (in-out and out-in). For type II transmembrane domain proteins, for which the N-terminal region is cytoplasmic, regions following the transmembrane domain is generally

extracellular. Secreted proteins on the other hand do not have a transmembrane domain and hence the whole protein is considered as extracellular.

[108] Membrane associated proteins can be engineered to delete the transmembrane domains, thus leaving the extracellular portions which can bind to ligands. Such soluble forms of transmembrane receptor proteins can be used to compete with natural forms for binding to ligand. Thus such soluble forms act as inhibitors. and can be used therapeutically as anti-angiogenic agents, as diagnostic tools for the quantification of natural ligands, and in assays for the identification of small molecules which modulate or mimic the activity of a TEM:ligand complex.

[109] Alternatively, the endothelial markers themselves can be used as vaccines to raise an immune response in the vaccinated animal or human. For such uses, a protein, or immunogenic fragment of such protein, corresponding to the intracellular, extracellular or secreted TEM of interest is administered to a subject. The immogenic agent may be provided as a purified preparation or in an appropriately expressing cell. The administration may be direct, by the delivery of the immunogenic agent to the subject, or indirect, through the delivery of a nucleic acid encoding the immunogenic agent under conditions resulting in the expression of the immunogenic agent of interest in the subject. The TEM of interest may be delivered in an expressing cell, such as a purified population of tumor endothelial cells or a populations of fused tumor endothelial and dendritic cells. Nucleic acids encoding the TEM of interest may be delivered in a viral or non-viral delivery vector or vehicle. Non-human sequences encoding the human TEM of interest or other mammalian homolog can be used to induce the desired immunologic response in a human subject. For several of the TEMs of the present invention, mouse, rat or other ortholog sequences are described herein or can be obtained from the literature or using techniques well within the skill of the art.

[110] Endothelial cells can be identified using the markers which are disclosed herein as being endothelial cell specific. These include the human markers

identified by SEQ ID NOS: 1-172, *i.e.,* the normal, pan-endothelial, and the tumor endothelial markers. Homologous mouse markers include tumor endothelial markers of SEQ ID NO: 182-186 and 190-194. Antibodies specific for such markers can be used to identify such cells, by contacting the antibodies with a population of cells containing some endothelial cells. The presence of cross-reactive material with the antibodies identifies particular cells as endothelial. Similarly, lysates of cells can be tested for the presence of cross-reactive material. Any known format or technique for detecting cross-reactive material can be used including, immunoblots, radioimmunoassay, ELISA, immunoprecipitation, and immunohistochemistry. In addition, nucleic acid probes for these markers can also be used to identify endothelial cells. Any hybridization technique known in the art including Northern blotting, RT-PCR, microarray hybridization, and in situ hybridization can be used.

[111] One can identify tumor endothelial cells for diagnostic purposes, testing cells suspected of containing one or more TEMs. One can test both tissues and bodily fluids of a subject. For example, one can test a patient's blood for evidence of intracellular and membrane associated TEMs, as well as for secreted TEMs. Intracellular and/or membrane associated TEMs may be present in bodily fluids as the result of high levels of expression of these factors and/or through lysis of cells expressing the TEMs.

[112] Populations of various types of endothelial cells can also be made using the antibodies to endothelial markers of the invention. The antibodies can be used to purify cell populations according to any technique known in the art, including but not limited to fluorescence activated cell sorting. Such techniques permit the isolation of populations which are at least 50, 60, 70, 80, 90, 92, 94, 95, 96, 97, 98, and even 99 % the type of endothelial cell desired, whether normal, tumor, or pan-endothelial. Antibodies can be used to both positively select and negatively select such populations. Preferably at least 1, 5, 10, 15, 20, or 25 of the appropriate markers are expressed by the endothelial cell population.

[113] Populations of endothelial cells made as described herein, can be used for screening drugs to identify those suitable for inhibiting the growth of tumors by virtue of inhibiting the growth of the tumor vasculature.

[114] Populations of endothelial cells made as described herein, can be used for screening candidate drugs to identify those suitable for modulating angiogenesis, such as for inhibiting the growth of tumors by virtue of inhibiting the growth of endothelial cells, such as inhibiting the growth of the tumor or other undesired vasculature, or alternatively, to promote the growth of endothelial cells and thus stimulate the growth of new or additional large vessel or microvasculature.

[115] Inhibiting the growth of endothelial cells means either regression of vasculature which is already present, or the slowing or the absence of the development of new vascularization in a treated system as compared with a control system. By stimulating the growth of endothelial cells, one can influence development of new (neovascularization) or additional vasculature development (revascularization). A variety of model screen systems are available in which to test the angiogenic and/or anti-angiogenic properties of a given candidate drug. Typical tests involve assays measuring the endothelial cell response, such as proliferation, migration, differentiation and/or intracellular interaction of a given candidate drug. By such tests, one can study the signals and effects of the test stimuli. Some common screens involve measurement of the inhibition of heparanase, endothelial tube formation on Matrigel, scratch induced motility of endothelial cells, platelet-derived growth factor driven proliferation of vascular smooth muscle cells, and the rat aortic ring assay (which provides an advantage of capillary formation rather than just one cell type).

[116] Drugs can be screened for the ability to mimic or modulate, inhibit or stimulate, growth of tumor endothelium cells and/or normal endothelial cells. Drugs can be screened for the ability to inhibit tumor endothelium growth but not normal endothelium growth or survival. Similarly, human cell

populations, such as normal endothelium populations or tumor endothelial cell populations, can be contacted with test substances and the expression of tumor endothelial markers and/or normal endothelial markers determined. Test substances which decrease the expression of tumor endothelial markers (TEMs) are candidates for inhibiting angiogenesis and the growth of tumors. Conversely, markers which are only expressed in normal endothelium but not in tumor endothelium (NEMs) can be monitored. Test substances which increase the expression of such NEMs in tumor endothelium and other human cells can be identified as candidate antitumor or anti-angiogenic drugs In cases where the activity of a TEM or NEM is known, agents can be screened for their ability to decrease or increase the activity.

[117] For those tumor endothelial markers identified as containing transmembrane regions, it is desirable to identify drug candidates capable of binding to the TEM receptors found at the cell surface. For some applications, the identification of drug candidates capable of blocking the TEM receptor from its native ligand will be desired. For some applications, the identification of a drug candidate capable of binding to the TEM receptor may be used as a means to deliver a therapeutic or diagnostic agent. For other applications, the identification of drug candidates capable of mimicing the activity of the native ligand will be desired. Thus, by manipulating the binding of a transmembrane TEM receptor:ligand complex, one may be able to promote or inhibit further development of endothelial cells and hence, vascularization.

[118] For those tumor endothelial markers identified as being secreted proteins, it is desirable to identify drug candidates capable of binding to the secreted TEM protein. For some applications, the identification of drug candidates capable of interfering with the binding of the secreted TEM it is native receptor. For other applications, the identification of drug candidates capable of mimicing the activity of the native receptor will be desired. Thus, by manipulating the binding of the secreted TEM:receptor complex, one may be able to promote or inhibit futher development of endothelial cells, and hence, vascularization.

[119] Expression can be monitored according to any convenient method. Protein or mRNA can be monitored. Any technique known in the art for monitoring specific genes' expression can be used, including but not limited to ELISAs, SAGE, microarray hybridization, Western blots. Changes in expression of a single marker may be used as a criterion for significant effect as a potential pro-angiogenic, anti-angiogenic or anti-tumor agent. However, it also may be desirable to screen for test substances which are able to modulate the expression of at least 5, 10, 15, or 20 of the relevant markers, such as the tumor or normal endothelial markers. Inhibition of TEM protein activity can also be used as a drug screen. Human and mouse TEMS can be used for this purpose.

[120] Test substances for screening can come from any source. They can be libraries of natural products, combinatorial chemical libraries, biological products made by recombinant libraries, etc. The source of the test substances is not critical to the invention. The present invention provides means for screening compounds and compositions which may previously have been overlooked in other screening schemes. Nucleic acids and the corresponding encoded proteins of the markers of the present invention can be used therapeutically in a variety of modes. NEMs, can be used to restrict, diminish, reduce, or inhibit proliferation of tumor or other abnormal or undesirable vasculature. TEMs can be used to stimulate the growth of vasculature, such as for wound healing or to circumvent a blocked vessel. The nucleic acids and encoded proteins can be administered by any means known in the art. Such methods include, using liposomes, nanospheres, viral vectors, non-viral vectors comprising polycations, etc. Suitable viral vectors include adenovirus, retroviruses, and sindbis virus. Administration modes can be any known in the art, including parenteral, intravenous, intramuscular, intraperitoneal, topical, intranasal, intrarectal, intrabronchial, etc.

[121] Specific biological antagonists of TEMs can also be used to therapeutic benefit. For example, antibodies, T cells specific for a TEM, antisense to a TEM, and ribozymes specific for a TEM can be used to restrict, inhibit,

reduce, and/or diminish tumor or other abnormal or undesirable vasculature growth. Such antagonists can be administered as is known in the art for these classes of antagonists generally. Anti-angiogenic drugs and agents can be used to inhibit tumor growth, as well as to treat diabetic retinopathy, rheumatoid arthritis, psoriasis, polycystic kidney disease (PKD), and other diseases requiring angiogenesis for their pathologies.

[122] Mouse counterparts to human TEMS can be used in mouse cancer models or in cell lines or *in vitro* to evaluate potential anti-angiogenic or anti-tumor compounds or therapies. Their expression can be monitored as an indication of effect. Mouse TEMs are disclosed in SEQ ID NO: 182-186 and 190-194. Mouse TEMs can be used as antigens for raising antibodies which can be tested in mouse tumor models. Mouse TEMs with transmembrane domains are particularly preferred for this purpose. Mouse TEMs can also be ued as vaccines to raise an immunological response in a human to the human ortholog.

[123] The above disclosure generally describes the present invention. All references disclosed herein are expressly incorporated by reference. A more complete understanding can be obtained by reference to the following specific examples which are provided herein for purposes of illustration only, and are not intended to limit the scope of the invention.

EXAMPLE 1

Visualization of vasculature of colorectal cancers

[124] The endothelium of human colorectal cancer was chosen to address the issues of tumor angiogenesis, based on the high incidence, relatively slow growth, and resistance to anti-neoplastic agents of these cancers. While certain less common tumor types, such as glioblastomas, are highly vascularized and are regarded as good targets for anti-angiogenic therapy, the importance of

angiogenesis for the growth of human colorectal cancers and other common solid tumor types is less well documented.

[125] We began by staining vessels in colorectal cancers using von Willebrand Factor (vWF) as a marker. In each of 6 colorectal tumors, this examination revealed a high density of vessels throughout the tumor parenchyma (Examples in Fig. 1 A and B). Interestingly, these analyses also substantiated the importance of these vessels for tumor growth, as endothelium was often surrounded by a perivascular cuff of viable cells, with a ring of necrotic cells evident at the periphery (Example in Fig. 1A). Although these preliminary studies suggested that colon tumors are angiogenesis-dependent, reliable markers that could distinguish vessels in colon cancers from the vessels in normal colon are currently lacking. One way to determine if such markers exist is by analyzing gene expression profiles in endothelium derived from normal and neoplastic tissue.

EXAMPLE 2

Purification of endothelial cells

[126] Global systematic analysis of gene expression in tumor and normal endothelium has been hampered by at least three experimental obstacles. First, endothelium is enmeshed in a complex tissue consisting of vessel wall components, stromal cells, and neoplastic cells, requiring highly selective means of purifying ECs for analysis. Second, techniques for defining global gene expression profiles were not available until recently. And third, only a small fraction of the cells within a tumor are endothelial, mandating the development of methods that are suitable for the analysis of global expression profiles from relatively few cells.

[127] To overcome the first obstacle, we initially attempted to purify ECs from dispersed human colorectal tissue using CD31, an endothelial marker

commonly used for this purpose. This resulted in a substantial enrichment of ECs but also resulted in contamination of the preparations by hematopoietic cells, most likely due to expression of CD31 by macrophages. We therefore developed a new method for purifying ECs from human tissues using P1H12, a recently described marker for ECs. Unlike CD31, P1H12 was specifically expressed on the ECs of both colorectal tumors and normal colorectal mucosa. Moreover, immunofluorescence staining of normal and cancerous colon with a panel of known cell surface endothelial markers (e.g. VE-cadherin, CD31 and CD34) revealed that P1H12 was unique in that it stained all vessels including microvessels (see Fig. 2A and data not shown). In addition to selection with P1H12, it was necessary to optimize the detachment of ECs from their neighbors without destroying their cell surface proteins as well as to employ positive and negative affinity purifications using a cocktail of antibodies (Fig. 2B). The ECs purified from normal colorectal mucosa and colorectal cancers were essentially free of epithelial and hematopoietic cells as judged by RT-PCR (Fig. 2C) and subsequent gene expression analysis (see below).

[128]

EXAMPLE 3

Comparison of tumor and normal endothelial cell expression patterns

[129] To overcome the remaining obstacles, a modification of the Serial Analysis of Gene Expression (SAGE) technique was used. SAGE associates individual mRNA transcripts with 14 base pair tags derived from a specific position near their 3' termini. The abundance of each tag provides a quantitative measure of the transcript level present within the mRNA population studied. SAGE is not dependent on pre-existing databases of expressed genes, and therefore provides an unbiased view of gene expression profiles. This feature is particularly important in the analysis of cells that constitute only a small fraction of the tissue under study, as transcripts from these cells are unlikely to be well represented in extant EST databases. We adapted the SAGE protocol so that it could be used on small numbers of

purified ECs obtained from the procedure outlined in Fig. 2B. A library of ~100,000 tags from the purified ECs of a colorectal cancer, and a similar library from the ECs of normal colonic mucosa from the same patient were generated. These ~193,000 tags corresponded to over 32,500 unique transcripts. Examination of the expression pattern of hematopoietic, epithelial and endothelial markers confirmed the purity of the preparations (Fig. 2D).

EXAMPLE 4

Markers of normal and tumor endothelium

[130] We next sought to identify Pan Endothelial Markers (PEMs), that is, transcripts that were expressed at significantly higher levels in both normal and tumor associated endothelium compared to other tissues. To identify such PEMs, tags expressed at similar levels in both tumor and normal ECs were compared to ~ 1.8 million tags from a variety of cell lines derived from tumors of non-endothelial origin. This simple comparison identified 93 transcripts that were strikingly EC-specific, i.e. expressed at levels at least 20-fold higher in ECs in vivo compared to non-endothelial cells in culture. The 15 tags corresponding to characterized genes which were most highly and specifically expressed in endothelium are shown in Table 1A. Twelve of these 15 most abundant endothelial transcripts had been previously shown to be preferentially expressed in endothelium , while the other 3 genes had not been associated with endothelium in the past (Table 1A). These data sets also revealed many novel PEMs, which became increasingly prevalent as tag expression levels decreased (Table 1B). For many of the transcripts, their endothelial origin was confirmed by SAGE analysis of ~401,000 transcripts derived from primary cultures of human umbilical vein endothelial cells (HUVEC) and human dermal microvascular endothelial cells (HMVEC) (Table 1 A and B). To further validate the expression of these PEMs in vivo, we developed a highly sensitive non-radioactive in situ hybridization method that allowed the detection of transcripts expressed at relatively low levels in frozen sections of human tissues. Two uncharacterized markers, PEM3 and

PEM6, were chosen for this analysis. In each case, highly specific expression was clearly limited to vascular ECs in both normal and neoplastic tissues (Fig. 3 A and B and data not shown). These data also suggest that ECs maintained in culture do not completely recapitulate expression patterns observed in vivo. For example, Hevin and several other PEM's were expressed at high levels in both tumor and normal ECs in vivo, but few or no transcripts were detected in cultured HUVEC or HMVEC (Table 1). The source of the Hevin transcripts was confirmed to be endothelium by in situ hybridization in normal and malignant colorectal tissue (Fig. 3C).

[131] Many of the markers reported in Table 1 were expressed at significantly higher levels than previously characterized genes commonly associated with ECs. For example, the top 25 markers were all expressed at greater than 200 copies per cell. In contrast, the receptors for VEGF (VEGFR-1 and VEGFR-2) were expressed at less than 20 copies per cell. Interestingly, VEGFR2 (KDR), which had previously been reported to be up-regulated in vessels during colon cancer progression , was found to be expressed in both normal and neoplastic colorectal tissue (Fig. 3 D and E). The lack of specificity of this gene was in accord with the SAGE data, which indicated that the VEGFR was expressed at 12 copies per cell in both normal and tumor endothelium.

EXAMPLE 5

Tumor *versus* normal endothelium

[132] We next attempted to identify transcripts that were differentially expressed in endothelium derived from normal or neoplastic tissues. This comparison revealed 33 tags that were preferentially expressed in normal-derived endothelium at levels at least 10-fold higher than in tumor-derived endothelium. Conversely, 46 tags were expressed at 10-fold or higher levels in tumor vessels. Because those transcripts expressed at higher levels in tumor endothelium are most likely to be useful in the future for diagnostic and therapeutic purposes, our subsequent studies focussed on this class. Of the top

25 tags most differentially expressed, 12 tags corresponded to 11 previously identified genes, one with an alternative polyadenylation site (see Table 2). Of these 10 genes, 6 have been recognized as markers associated with angiogenic vessels. The remaining 14 tags corresponded to uncharacterised genes, most of which have only been deposited as ESTs (Table 2).

[133] To validate the expression patterns of these genes, we chose to focus on 9 Tumor Endothelial Markers (BSC-TEM 1-9; TEM 1, 2, 5, 9, 16, 17, 19, and 22) for which EST sequences but no other information was available (Table 2). These tags were chosen simply because they were among the most differentially expressed on the list and because we were able to obtain suitable probes. In many cases, this required obtaining near full-length sequences through multiple rounds of sequencing and cDNA walking (See accession numbers in Table 2). RT-PCR analysis was then used to evaluate the expression of the corresponding transcripts in purified ECs derived from normal and tumor tissues of two patients different from the one used to construct the SAGE libraries. As shown in Fig. 4 A, the vWF gene, expected to be expressed in both normal and tumor endothelium on the basis of the SAGE data as well as previous studies, was expressed at similar levels in normal and tumor ECs from both patients, but was not expressed in purified tumor epithelial cells. As expected, PEM2 displayed a pattern similar to vWF. In contrast, all 9 TEMs chosen for this analysis were prominently expressed in tumor ECs, but were absent or barely detectable in normal ECs (Table 3 and examples in Fig. 4A). It is important to note that these RT-PCR assays were extremely sensitive indicators of expression, and the absence of detectable transcripts in the normal endothelium, combined with their presence in tumor endothelial RNAs even when diluted 100-fold, provides compelling confirmatory evidence for their differential expression. These results also show that these transcripts were not simply expressed differentially in the ECs of the original patient, but were characteristic of colorectal cancer endothelium in general.

[134] It could be argued that the results noted above were compromised by the possibility that a small number of non-endothelial cells contaminated the cell populations used for SAGE and RT-PCR analyses, and that these non-endothelial cells were responsible for the striking differences in expression of the noted transcripts. To exclude this possibility, we performed in situ hybridization on normal and neoplastic colon tissue. In every case where transcripts could be detected (BSC-TEM 1, 3, 4, 5, 7, 8, and 9; TEM 1, 5, 9, 17, and 19), they were specifically localized to ECs (Table 3 and examples in Fig. 4 B and C). Although caution must be used when interpreting negative in situ hybridization results, none of the TEMs were expressed in vascular ECs associated with normal colorectal tissue even though vWF and Hevin were clearly expressed (Table 3).

EXAMPLE 6

Tumor endothelium markers are expressed in multiple tumor types

[135] Were these transcripts specifically expressed in the endothelium within primary colorectal cancers, or were they characteristic of tumor endothelium in general? To address this question, we studied the expression of a representative TEM (BSC-TEM7; TEM 17) in a liver metastasis from a colorectal cancer, a sarcoma, and in primary cancers of the lung, pancreas, breast and brain. As shown in Fig. 4, the transcript was found to be expressed specifically in the endothelium of each of these cancers, whether metastatic (Fig. 4D) or primary (Fig. 4E-I). Analysis of the other six TEMs, (BSC-TEM 1, 3,4,5, 7, 8 and 9; TEM 1, 5, 9, 17, and 19) revealed a similar pattern in lung tumors, brain tumors, and metastatic lesions of the liver (see Table 3).

EXAMPLE 7

Tumor endothelium markers are neo-angiogenic

[136] Finally, we asked whether these transcripts were expressed in angiogenic states other than that associated with tumorigenesis. We thus performed in situ hybridizations on corpus luteum tissue as well as healing wounds. Although there were exceptions, we found that these transcripts were generally expressed both in the corpus luteum and in the granulation tissue of healing wounds (Table 3 and example in Fig. 4J). In all tissues studied, expression of the genes was either absent or exclusively confined to the EC compartment.

References and Notes

The disclosure of each reference cited is expressly incorporated herein.

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8. The original EC isolation protocol was the same as that shown in Fig. 2B except that dispersed cells were stained with anti-CD31 antibodies instead of anti-P1H12, and magnetic beads against CD64 and CD14 were not included in the negative selection. After generating 120,000 SAGE tags from these two EC preparations, careful analysis of the SAGE data revealed that, in addition to endothelial-specific markers, several macrophage-specific markers were also present.

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11. In order to reduce the minimum amount of starting material required from ~50 million cells to ~50,000 cells (i.e. ~1000-fold less) we and others (38) have introduced several modifications to the original SAGE protocol. A detailed version of our modified "MicroSAGE" protocol is available from the authors upon request.

12. 96,694 and 96,588 SAGE tags were analyzed from normal and tumor derived ECs, respectively, and represented 50,298 unique tags. A conservative estimate of 32,703 unique transcripts was derived by considering only those tags observed more than once in the current data set or in the 134,000 transcripts previously identified in human transcriptomes (39).

13. To identify endothelial specific transcripts, we normalized the number of tags analyzed in each group to 100,000, and limited our analysis to transcripts that were expressed at levels at least 20-fold higher in ECs than in non-endothelial cell lines in culture and present at fewer than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic fraction (~57,000 tags)(41). Non-endothelial cell lines consisted of 1.8x106 tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. A complete list of PEMs is available at www.sagenet.org\angio\table1.htm.

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26. For non-radioactive in situ hybridization, digoxigenin (DIG)-labelled sense and anti-sense riboprobes were generated through PCR by amplifying 500-600 bp products and incorporating a T7 promoter into the anti-sense primer. In vitro transcription was performed using DIG RNA labelling reagents and T7 RNA polymerase (Roche, Indianapolis, IN). Frozen tissue sections were fixed with 4 % paraformaldehyde, permeabilized with pepsin, and incubated with 200 ng/ml of riboprobe overnight at 55oC. For signal amplification, a horseradish peroxidase (HRP) rabbit anti-DIG antibody (DAKO, Carpinteria, CA) was used to catalyse the deposition of Biotin-Tyramide (from GenPoint kit, DAKO). Further amplification was achieved by adding HRP rabbit anti-biotin (DAKO), biotin-tyramide, and then alkaline-phosphatase (AP) rabbit anti-biotin (DAKO). Signal was detected using the AP substrate Fast Red TR/Napthol AS-MX (Sigma, St. Louis, MO), and cells were counterstained with hematoxylin unless otherwise indicated. A detailed protocol including the list of primers used to generate the probes can be obtained from the authors upon request.

27. Transcript copies per cell were calculated assuming an average cell contains 300,000 transcripts.

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31. Endothelial-specific transcripts were defined as those expressed at levels at least 5-fold higher in ECs in vivo than in non-endothelial cell lines in culture (13), and present at no more than 5 copies per 100,000 transcripts in non-endothelial cell lines and the hematopoietic cell fraction (41). Transcripts showing statistically different levels of expression (P <0.05) were then identified using Monte Carlo analysis as previously described (40). Transcripts preferentially expressed in normal endothelium were then defined as those expressed at levels at least 10-fold higher in normal endothelium than in tumor endothelium. Conversely, tumor endothelial transcripts were at least 10-fold higher in tumor versus normal endothelium. See www.sagenet.org\angio\table2.htm and www.sagenet.org\angio\table3.htm for a complete list of differentially expressed genes.

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41. Human colon tissues were obtained within ½ hour after surgical removal from patients. Sheets of epithelial cells were peeled away from normal tissues with a glass slide following treatment with 5 mM DDT, then 10 mM EDTA, leaving the lamina propria intact. After a 2h incubation in collagenase at 37 oC, cells were filtered

sequentially through 400 um, 100 um, 50 um and 25 um mesh, and spun through a 30 % pre-formed Percoll gradient to pellet RBCs. Epithelial cells (Epithelial Fraction), which were found to non-specifically bind magnetic beads, were removed using Dynabeads coupled to BerEP4 (Dynal, Lake Success, NY). Subsequently, macrophages and other leukocytes (Hematopoietic Fraction) were removed using a cocktail of beads coupled to anti-CD45, anti-CD14 and anti-CD64 (Dynal). The remaining cells were stained with P1H12 antibody, purified with anti-mouse IgG-coupled magnetic beads, and lysed in mRNA lysis buffer. A detailed protocol can be obtained from the authors upon request.

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Sequence name	SEQ ID NO:
PEM 1	1
PEM 2	2
PEM 3	3
PEM 4	4
PEM 5	5
PEM 6	6
PEM 7	7
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PEM 10	10
PEM 11	11
PEM 12	12
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PEM 14	14
PEM 15	15
PEM 16	16
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PEM 34	34
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PEM 37	37
PEM 38	38

SEQ ID NO:	Sequence name
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TEM 5 DNA	180
TEM 7B DNA	181
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mTEM 5 DNA	183
mTEM 7 DNA	184
mTEM 7B DNA	185
mTEM 8 DNA	186
TEM 8 Protein	187
TEM 5 Protein	188
TEM 7B Protein	189
mTEM 1 Protein	190
mTEM 5 Protein	191
mTEM 7 Protein	192
mTEM 7b Protein	193
mTEM 8 Protein	194
TEM 1 DNA	195
TEM 1 Protein	196
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357	TEM 46 long tag
358	TEM 35 Protein
359	TEM 3 DNA with 5'UTR

CLAIMS

1. An isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of TEM 3 protein as shown in SEQ ID NO: 200.
2. The isolated molecule of claim 1 which is an in tact antibody molecule.
3. The isolated molecule of claim 1 which is a single chain variable region (ScFv).
4. The isolated molecule of claim 1 which is a monoclonal antibody.
5. The isolated molecule of claim 1 which is a humanized antibody.
6. The isolated molecule of claim 1 which is a human antibody.
7. The isolated molecule of claim 1 which is bound to a cytotoxic moiety.
8. The isolated molecule of claim 1 which is bound to a therapeutic moiety.
9. The isolated molecule of claim 1 which is bound to a detectable moiety.
10. The isolated molecule of claim 1 which is bound to an anti-tumor agent.
11. A method of inhibiting neoangiogenesis, comprising:

    administering to a subject in need thereof an effective amount of an isolated molecule comprising an antibody

variable region which specifically binds to an extracellular domain of TEM 3 protein as shown in SEQ ID NO: 200, whereby neoangiogenesis is inhibited.

12. The method of claim 11 wherein the subject bears a vascularized tumor.

13. The method of claim 11 wherein the subject has polycystic kidney disease.

14. The method of claim 11 wherein the subject has diabetic retinopathy.

15. The method of claim 11 wherein the subject has rheumatoid arthritis.

16. The method of claim 11 wherein the subject has psoriasis.

17. A method of inhibiting tumor growth, comprising:

administering to a human subject bearing a tumor an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of TEM 3 protein as shown in SEQ ID NO: 200, whereby growth of the tumor is inhibited.

18. An isolated molecule comprising an antibody variable region which specifically binds to TEM 3 protein as shown in SEQ ID NO: 200.

19. The isolated molecule of claim 18 which is a single chain variable region (ScFv).

20. The isolated molecule of claim 18 which is a monoclonal antibody.

21. The isolated molecule of claim 18 which is a humanized antibody.

22. The isolated molecule of claim 18 which is a human antibody.

23. The isolated molecule of claim 18 which is bound to a cytotoxic moiety.

24. The isolated molecule of claim 18 which is bound to a therapeutic moiety.

25. The isolated molecule of claim 18 which is bound to a detectable moiety.

26. The isolated molecule of claim 18 which is bound to an anti-tumor agent.

27. The isolated molecule of claim 18 which is an in tact antibody molecule.

28. An isolated and purified human transmembrane protein: TEM 3, as shown in SEQ ID NO: 200.

29. An isolated and purified nucleic acid molecule comprising a coding sequence for a transmembrane TEM 3 as shown in SEQ ID NO: 200.

30. The isolated and purified nucleic acid molecule of claim 29 which comprises a coding sequence selected from those shown in SEQ ID NO: 199 and 359.

31. A recombinant host cell which comprises a nucleic acid molecule comprising a coding sequence for a transmembrane TEM 3 as shown in SEQ ID NO: 200.

32. The recombinant host cell of claim 31 which comprises a coding sequence selected from those shown in SEQ ID NO: 199 and 359.

33. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a nucleic acid molecule comprising a coding sequence for a human transmembrane protein TEM 3 as shown in SEQ ID NO: 200, whereby an immune response to the human transmembrane protein is induced in the mammal.

34. The method of claim 33 wherein the coding sequence is shown in SEQ ID NO: 199.

35. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a purified human transmembrane protein TEM 3as shown in SEQ ID NO: 200, whereby an immune response to the human transmembrane protein is induced in the mammal.

36. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with an isolated and purified human trasmembrane protein TEM 3 as shown in SEQ ID NO: 200;

contacting the isolated and purified human trasmembrane protein with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein 3, as shown in SEQ ID NO: 200;

determining binding of the molecule comprising an antibody variable region to the human transmembrane protein, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the human transmembrane protein is identified as a ligand involved in endothelial cell regulation.

37. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with a cell comprising a human transmembrane protein 3 as shown in SEQ ID NO: 200;

contacting the cell with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein selected from the group consisting of: 3 as shown in SEQ ID NO:200;

determining binding of the molecule comprising an antibody variable region to the cell, wherein a test compound which diminishes the binding of the molecule comprising an antibody variable region to the cell is identified as a ligand involved in endothelial cell regulation.

38. A soluble form of a human transmembrane protein TEM 3 as shown in SEQ ID NO: 200, respectively, wherein the soluble forms lack transmembrane domains.

39. The soluble form of claim 38 wherein the soluble form consists of an extracellular domain of the human transmembrane protein.

40. A method of inhibiting neoangiogenesis in a patient, comprising:

administering to the patient a soluble form of a human transmembrane protein according to claim 38, whereby neoangiogenesis in the patient is inhibited.

41. A method of inhibiting neoangiogenesis in a patient, comprising:

administering to the patient a soluble form of a human transmembrane protein according to claim 39, whereby neoangiogenesis in the patient is inhibited.

42. The method of claim 40 wherein the patient bears a vascularized tumor.

43. The method of claim 41 wherein the patient bears a vascularized tumor.

44. The method of claim 40 wherein the patient has polycystic kidney disease.

45. The method of claim 40 wherein the patient has diabetic retinopathy.

46. The method of claim 40 wherein the patient has rheumatoid arthritis.

47. The method of claim 40 wherein the patient has psoriasis.

48. The method of claim 41 wherein the patient has polycystic kidney disease.

49. The method of claim 41 wherein the patient has diabetic retinopathy.

50. The method of claim 41 wherein the patient has rheumatoid arthritis.

51. The method of claim 41 wherein the patient has psoriasis.

52. A method of identifying regions of neoangiogenesis in a patient, comprising:

administering to a patient a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein 3 as shown in SEQ ID NO: 200, wherein the molecule is bound to a detectable moiety; and

detecting the detectable moiety in the pateint, thereby identifying neoangiogenesis.

53. A method of screening for neoangiogenesis in a patient, comprising:

contacting a body fluid collected from the patient with a molecule comprising an antibody variable region which specifically binds to an extracellular domain of a TEM protein 3 as shown in SEQ ID NO: 200, wherein detection of cross-reactive material in the body fluid with the molecule indicates neoangiogenesis in the patient.

54. A method of inducing an immune response to tumor endothelial cells in a patient, comprising:

administering to a patient in need thereof a mouse TEM protein selected from the group consisting of: 1, 2, 3, 9, 13, 17, 19, 22, and 30 as shown in SEQ ID NO: 291, 293, 299, 295, 303, 297, 301, 305, and 307, whereby an immune response to a human TEM protein is induced.

55. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express TEM 3 gene as shown in SEQ ID NO: 199 with a test compound;

determining expression of said one or more TEM genes by hybridization of mRNA of said cells to a nucleic acid probe which is complementary to said mRNA; and

identifying a test compound as a candidate drug for treating tumors if it decreases expression of said one or more TEM genes.

56. The method of claim 55 wherein the cells are endothelial cells.

57. The method of claim 55 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

58. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express TEM 3 protein as shown in SEQ ID NO: 200, with a test compound;

determining amount of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the amount of one more TEM proteins in said cells.

59. The method of claim 58 wherein the cells are endothelial cells.

60. The method of claim 58 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

61. A method to identify candidate drugs for treating tumors, comprising:

contacting cells which express TEM 3 protein as shown in SEQ ID NO: 200 with a test compound;

determining activity of said one or more TEM proteins in said cells; and

identifying a test compound as a candidate drug for treating tumors if it decreases the activity of of one more TEM proteins in said cells.

62. The method of claim 61 wherein the cells are endothelial cells.

63. The method of claim 61 wherein the cells are recombinant host cells which are transfected with an expression construct which encodes said one or more TEMs.

64. A method to identify candidate drugs for treating patients bearing tumors, comprising:

contacting a test compound with recombinant host cells which are transfected with an expession construct which encodes TEM 3 proteinas shown in SEQ ID NO: 200;

determining proliferation of said cells; and

identifying a test compound which inhibits proliferation of said cells as a candidate drug for treating patients bearing tumors.

65. A method for identification of a ligand involved in endothelial cell regulation, comprising:

contacting a test compound with a human transmembrane protein TEM 3 as shown in SEQ ID NO: 200;

determining binding of a test compound to the human transmembrane protein, wherein a test compound which binds to the protein is identified as a ligand involved in endothelial cell regulation.

66. A method of inducing an immune response in a mammal, comprising:

administering to the mammal a cell which expresses a transmembrane protein TEM 3 as shown in SEQ ID NO: 200, wherein the cell is a recombinant cell which comprises a vector econding said transmembrane protein, or the cell is a fusion of a dendritic cell and a tumor endothelium cell, whereby an immune response to the human transmembrane protein is induced in the mammal.

67. A method of inhibiting neoangiogenesis, comprising:

administering to a subject in need thereof an effective amount of an isolated molecule comprising an antibody variable region which specifically binds to an extracellular domain of a mouse TEM protein selected from the group

consisting of: 1, 2, 3, 9, 17, and 19, as shown in SEQ ID NO: 291, 293, 299, 295, 297, and 301, respectively, whereby neoangiogenesis is inhibited.

68. The method of claim 87 wherein the subject is a mouse.
69. The method of claim 87 wherein the subject bears a vascularized tumor.
70. The method of claim 87 wherein the subject has polycystic kidney disease.
71. The method of claim 87 wherein the subject has diabetic retinopathy.
72. The method of claim 87 wherein the subject has rheumatoid arthritis.
73. The method of claim 87 wherein the subject has psoriasis.

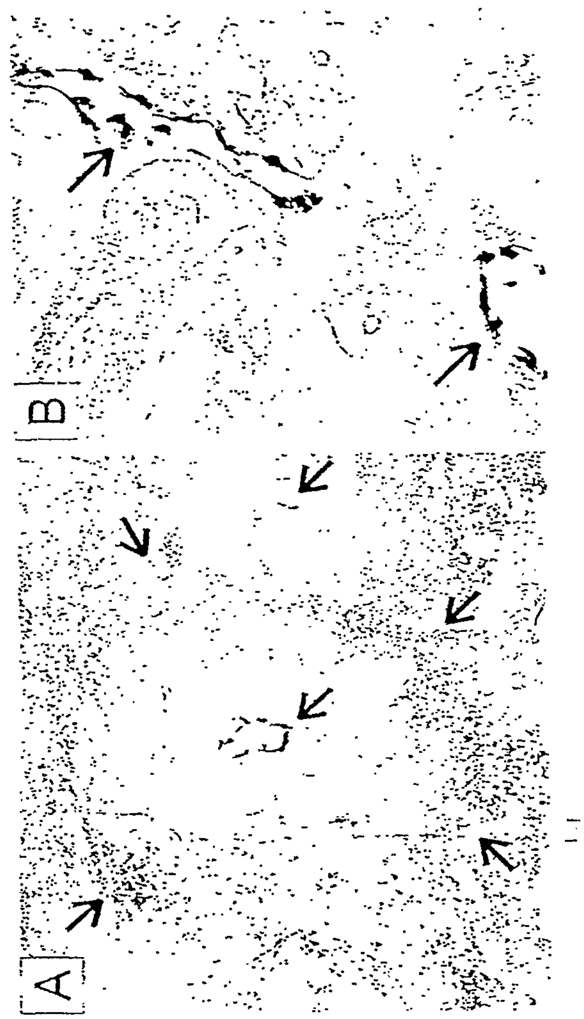
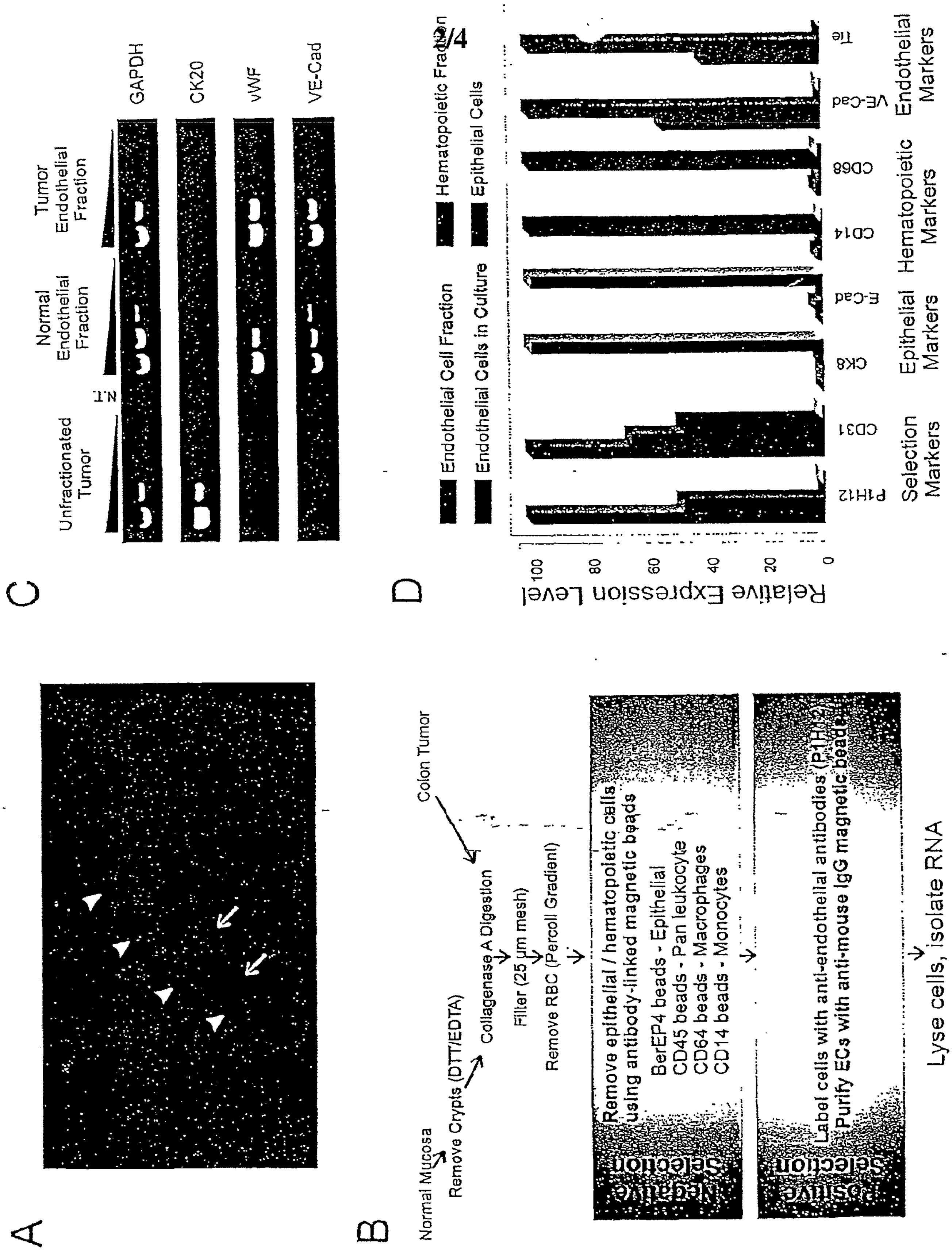


Figure 1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BerEP4 beads - Epithelial
CD45 beads - Pan leukocyte
CD64 beads - Macrophages
CD14 beads - Monocytes
Positive Selection
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Purify ECs with anti-mouse IgG magnetic beads
Lyse cells, isolate RNA
C
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N.T.
Normal Endothelial Fraction
Tumor Endothelial Fraction
GAPDH
CK20
vWF
VE-Cad
D
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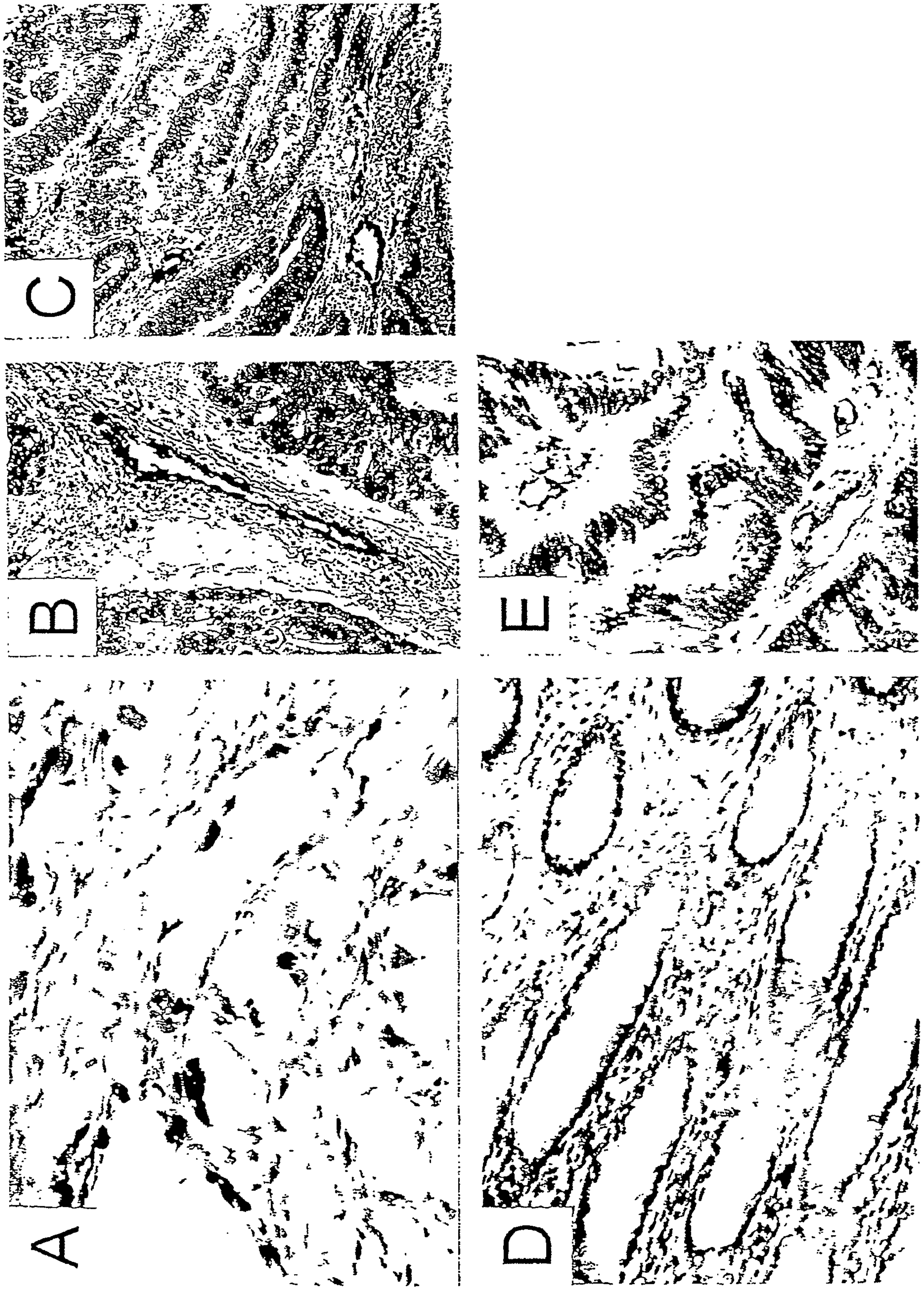
Figure 2



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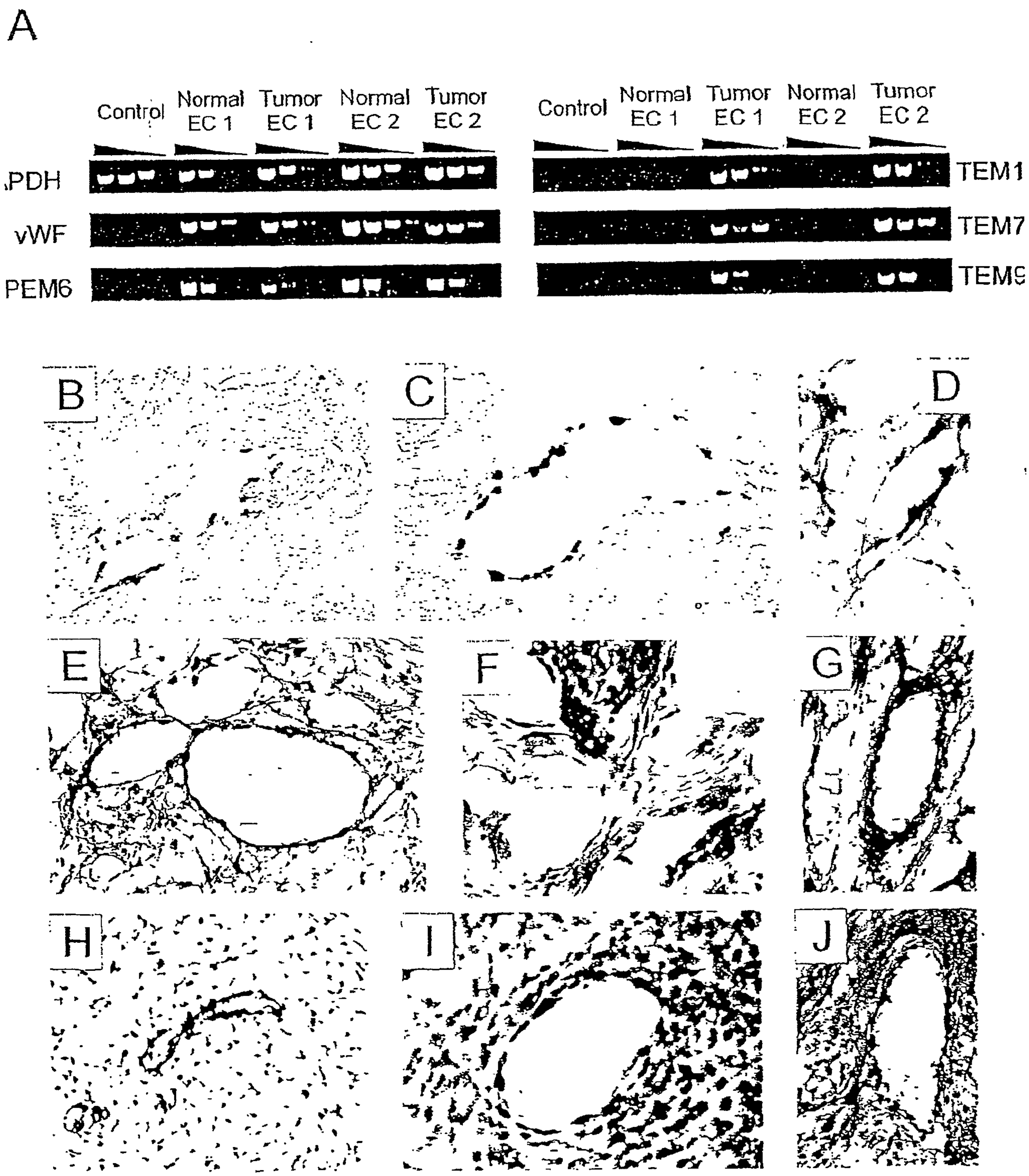
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Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu Ser Arg Asp His
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Leu Gly Ala Gln Leu Pro Pro Gln Ala Pro Asp Ala Leu Val Leu Arg
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Pro Ala Ala Thr Gln Pro Ala Ala Leu Pro Thr Leu Leu Pro Ser Gln
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Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
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Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly Asp Met Tyr Gln
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Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe Pro Ala Met Arg
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Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu Val Phe Ser Leu
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Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu Gln Lys Gln Ile
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Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val Ser Gly Asp Glu
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Ser Gly Trp Ala Ala Lys Gly Thr Val Arg Gly Trp Asn Arg Arg Ala
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Gln Asp Leu Gly Gly Gly Thr Leu Ala Met Asp Thr Leu Pro Asp Asn
65                  70                  75                  80
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Tyr Gly Pro Ser Glu Pro His Ser Arg Glu Leu Trp Val Asp Val Ala
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Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile Phe
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Met Gly Asp Val Ile His Arg Met Leu Thr Ala Thr Gln Tyr Val Ala
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Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr Val
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Val Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His Val
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675 680 685
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Val Gln Trp Asp His Val Tyr Leu Gln Gly Trp Glu Asp Lys Gly Ser
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<212> PRT
<213> Homo sapiens

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35 40 45
Leu Asp Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr
50 55 60
Phe Val Glu Gln Leu Ala His Lys Phe Ile Ser Pro Gln Leu Arg Met
65 70 75 80
Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
85 90 95
Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
100 105 110
Leu Pro Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser
115 120 125

Glu Gln Ile Tyr Tyr Glu Asn Arg Gln Gly Tyr Arg Thr Ala Ser Val
130 135 140
Ile Ile Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr
145 150 155 160
Ser Glu Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr
165 170 175
Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
180 185 190
Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
195 200 205
Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
210 215 220
Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
225 230 235 240
Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
245 250 255
Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
260 265 270
Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
275 280 285
Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
290 295 300
Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
305 310 315 320
Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
325 330 335
Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
340 345 350
Glu Val Pro Pro Pro Pro Ala Glu Glu Ser Glu Glu Glu Asp Asp Asp
355 360 365
Gly Leu Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly
370 375 380
Gly Arg Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu
385 390 395 400
Lys Gly Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala
405 410 415
Arg Val Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn
420 425 430
Leu Asn Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser
435 440 445
Pro Ile Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly
450 455 460
Tyr Asp Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg
465 470 475 480
Cys Ile Asn Phe Thr Arg Val Lys Asn Asn Gln Pro Ala Lys Tyr Pro
485 490 495
Leu Asn Asn Ala Tyr His Thr Ser Ser Pro Pro Pro Ala Pro Ile Tyr
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Thr Pro Pro Pro Pro Ala Pro His Cys Pro Pro Pro Pro Pro Ser Ala
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<212> PRT
<213> Homo sapiens

<400> 188
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Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
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Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
65                  70                  75                  80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
                85                  90                  95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
            100                 105                 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
        115                 120                 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
    130                 135                 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145                 150                 155                 160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
                165                 170                 175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
            180                 185                 190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
        195                 200                 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
    210                 215                 220
Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr
225                 230                 235                 240
His His Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
                245                 250                 255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
            260                 265                 270
Arg Trp Tyr His Asn Arg Ala Pro Val Glu Gly Asp Glu Gln Ala Gly
        275                 280                 285
Ile Leu Leu Ala Glu Ser Leu Ile His Asp Cys Thr Phe Ile Thr Ser
    290                 295                 300
Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305                 310                 315                 320
Cys Thr Val Ser Met Ala Gln Gly Asn Ala Ser Lys Lys Val Glu Ile
                325                 330                 335
Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Ala
            340                 345                 350
Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
        355                 360                 365
Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Gly
    370                 375                 380
Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
385                 390                 395                 400
Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
                405                 410                 415
Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
            420                 425                 430
Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
        435                 440                 445
Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
    450                 455                 460
Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
465                 470                 475                 480
Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
                485                 490                 495
Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Arg Ile Val Gly Ala Leu
            500                 505                 510
Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
        515                 520                 525
Val Asn Ala Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
    530                 535                 540
Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Gly Gly
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Pro Glu Pro Pro Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
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Arg Pro Asn Val Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
        595                 600                 605
Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Ser Leu Pro Ala
    610                 615                 620
Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
625                 630                 635                 640
Phe Arg Asn Gly Arg Leu Phe His Ser His Ser Asn Thr Ser Arg Pro
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Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val Ile
            660                 665                 670
Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro Val
        675                 680                 685
Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Glu Pro Val Ala Ala
    690                 695                 700
Trp Trp Ser Gln Glu Gly Pro Gly Glu Ala Gly Gly Trp Thr Ser Glu
705                 710                 715                 720
Gly Cys Gln Leu Arg Ser Ser Gln Pro Asn Val Ser Ala Leu His Cys
                725                 730                 735
Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
            740                 745                 750
Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
        755                 760                 765
Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
    770                 775                 780
Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
785                 790                 795                 800
Leu Leu Asn Leu Cys Phe His Ile Ala Met Thr Ser Ala Val Phe Ala
                805                 810                 815
Gly Gly Ile Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly
            820                 825                 830
Ile Thr Leu His Tyr Ser Ser Leu Ser Thr Leu Leu Trp Met Gly Val
        835                 840                 845
Lys Ala Arg Val Leu His Lys Glu Leu Thr Trp Arg Ala Pro Pro Pro
    850                 855                 860
Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe
865                 870                 875                 880
Tyr Leu Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala
                885                 890                 895
Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu
            900                 905                 910
Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile
        915                 920                 925
Leu Leu Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu Arg Leu Arg
    930                 935                 940
Gly Pro Leu Ala Gln Asn Pro Lys Ala Gly Asn Ser Arg Ala Ser Leu
945                 950                 955                 960
Glu Ala Gly Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Gly Ser Gly
                965                 970                 975
Pro Leu Leu Ser Asp Ser Gly Ser Leu Leu Ala Thr Gly Ser Ala Arg
            980                 985                 990
Val Gly Thr Pro Gly Pro Pro Glu Asp Gly Asp Ser Leu Tyr Ser Pro
        995                 1000                1005
Gly Val Gln Leu Gly Ala Leu Val Thr Thr His Phe Leu Tyr Leu Ala
    1010                1015                1020
Met Trp Ala Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg
1025                1030                1035                1040
Val Val Cys Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu
                1045                1050                1055
Phe Val Phe Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser
            1060                1065                1070
Trp Arg Ala Cys Cys Pro Pro Ala Ser Pro Ala Ala Pro His Ala Pro
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Pro Arg Ala Leu Pro Ala Ala Ala Glu Asp Gly Ser Pro Val Phe Gly
1090 1095 1100
Glu Gly Pro Pro Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly His
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Pro Leu Ala Leu Gly Pro Cys Lys Leu Thr Asn Leu Gln Leu Ala Gln
1125 1130 1135
Ser Gln Val Cys Glu Ala Gly Ala Ala Ala Gly Gly Glu Gly Glu Pro
1140 1145 1150
Glu Pro Ala Gly Thr Arg Gly Asn Leu Ala His Arg His Pro Asn Asn
1155 1160 1165
Val His His Gly Arg Arg Ala His Lys Ser Arg Ala Lys Gly His Arg
1170 1175 1180
Ala Gly Glu Ala Cys Gly Lys Asn Arg Leu Lys Ala Leu Arg Gly Gly
1185 1190 1195 1200
Ala Ala Gly Ala Leu Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His
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Asn Ser Pro Thr Asp Ser Tyr Leu Gly Ser Ser Arg Asn Ser Pro Gly
1220 1225 1230
Ala Gly Leu Gln Leu Glu Gly Glu Pro Met Leu Thr Pro Ser Glu Gly
1235 1240 1245
Ser Asp Thr Ser Ala Ala Pro Leu Ser Glu Ala Gly Arg Ala Gly Gln
1250 1255 1260
Arg Arg Ser Ala Ser Arg Asp Ser Leu Lys Gly Gly Gly Ala Leu Glu
1265 1270 1275 1280
Lys Glu Ser His Arg Arg Ser Tyr Pro Leu Asn Ala Ala Ser Leu Asn
1285 1290 1295
Gly Ala Pro Lys Gly Gly Lys Tyr Asp Asp Val Thr Leu Met Gly Ala
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Thr Thr Val
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<210> 189
<211> 529
<212> PRT
<213> Homo sapiens

<400> 189
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35 40 45
His Thr Glu Glu Glu Val Glu Val Asp Ser His Ala Tyr Ser His Arg
50 55 60
Trp Lys Arg Asn Leu Asp Phe Leu Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Val Gly Gln Asp Ser Pro Glu Pro Arg Ser Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ser Asp Ser Ala Ser
115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Arg Glu Ile Thr
165 170 175
Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205

Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
275 280 285
Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
290 295 300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
305 310 315 320
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
325 330 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
340 345 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
355 360 365
Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
370 375 380
Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
385 390 395 400
Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
405 410 415
Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
420 425 430
Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
435 440 445
Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
450 455 460
Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
465 470 475 480
Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
485 490 495
Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
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Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu Gln
515 520 525
Cys

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<212> PRT
<213> Mus musculus

<400> 190
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35 40 45
Arg Ala Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro
50 55 60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn
65 70 75 80
Gly Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro
85 90 95
Gln Arg Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr
100 105 110
Ala Phe Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala
115 120 125
Gln Arg Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu

130 135 140
Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
145 150 155 160
Glu Gly Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro
165 170 175
Ala Val Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp
180 185 190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
195 200 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser
210 215 220
Gln Thr Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly
225 230 235 240
Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly Ala Val Ser Cys
245 250 255
Arg Cys Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu
260 265 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
275 280 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
290 295 300
Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
305 310 315 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
325 330 335
Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
340 345 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Arg Asp Glu Leu
355 360 365
Leu Asp Asp Gly Glu Glu Gly Glu Asp Glu Glu Glu Pro Trp Glu Asp
370 375 380
Phe Asp Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro
385 390 395 400
Thr His Pro Pro Asp Phe Gly Leu Pro Tyr Arg Pro Asn Phe Pro Gln
405 410 415
Asp Gly Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro
420 425 430
Leu Ser Ala Pro Arg Gly Pro Tyr His Ser Ser Val Val Ser Ala Thr
435 440 445
Arg Pro Met Val Ile Ser Ala Thr Arg Pro Thr Leu Pro Ser Ala His
450 455 460
Lys Thr Ser Val Ile Ser Ala Thr Arg Pro Pro Leu Ser Pro Val His
465 470 475 480
Pro Pro Ala Met Ala Pro Ala Thr Pro Pro Ala Val Phe Ser Glu His
485 490 495
Gln Ile Pro Lys Ile Lys Ala Asn Tyr Pro Asp Leu Pro Phe Gly His
500 505 510
Lys Pro Gly Ile Thr Ser Ala Thr His Pro Ala Arg Ser Pro Pro Tyr
515 520 525
Gln Pro Pro Ile Ile Ser Thr Asn Tyr Pro Gln Val Phe Pro Pro His
530 535 540
Gln Ala Pro Met Ser Pro Asp Thr His Thr Ile Thr Tyr Leu Pro Pro
545 550 555 560
Val Pro Pro His Leu Asp Pro Gly Asp Thr Thr Ser Lys Ala His Gln
565 570 575
His Pro Leu Leu Pro Asp Ala Pro Gly Ile Arg Thr Gln Ala Pro Gln
580 585 590
Leu Ser Val Ser Ala Leu Gln Pro Pro Leu Pro Thr Asn Ser Arg Ser
595 600 605
Ser Val His Glu Thr Pro Val Pro Ala Ala Asn Gln Pro Pro Ala Phe
610 615 620
Pro Ser Ser Pro Leu Pro Pro Gln Arg Pro Thr Asn Gln Thr Ser Ser
625 630 635 640
Ile Ser Pro Thr His Ser Tyr Ser Arg Ala Pro Leu Val Pro Arg Glu
645 650 655
Gly Val Pro Ser Pro Lys Ser Val Pro Gln Leu Pro Ser Val Pro Ser

660 665 670
Thr Ala Ala Pro Thr Ala Leu Ala Glu Ser Gly Leu Ala Gly Gln Ser
675 680 685
Gln Arg Asp Asp Arg Trp Leu Leu Val Ala Leu Leu Val Pro Thr Cys
690 695 700
Val Phe Leu Val Val Leu Leu Ala Leu Gly Ile Val Tyr Cys Thr Arg
705 710 715 720
Cys Gly Ser His Ala Pro Asn Lys Arg Ile Thr Asp Cys Tyr Arg Trp
725 730 735
Val Thr His Ala Gly Asn Lys Ser Ser Thr Glu Pro Met Pro Pro Arg
740 745 750
Gly Ser Leu Thr Gly Val Gln Thr Cys Arg Thr Ser Val
755 760 765

<210> 191
<211> 1329
<212> PRT
<213> Mus musculus

<400> 191
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Pro Ile Arg Gly Cys Lys Cys Ser Gly Glu Arg Pro Lys Gly Leu Ser
35 40 45
Gly Gly Ala His Asn Pro Ala Arg Arg Arg Val Val Cys Gly Gly Gly
50 55 60
Asp Leu Pro Glu Pro Pro Asp Pro Gly Leu Leu Pro Asn Gly Thr Ile
65 70 75 80
Thr Leu Leu Leu Ser Asn Asn Lys Ile Thr Gly Leu Arg Asn Gly Ser
85 90 95
Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Ser Asn Val
100 105 110
Ile Ser Thr Val Gln Pro Gly Ala Phe Leu Gly Leu Gly Glu Leu Lys
115 120 125
Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
130 135 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145 150 155 160
Tyr Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
165 170 175
Ile Val Asp Phe Gly Thr Glu Phe Leu Thr Cys Asp Cys Arg Leu Arg
180 185 190
Trp Leu Leu Pro Trp Ala Arg Asn His Ser Leu Gln Leu Ser Glu Arg
195 200 205
Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala His Ala Leu Ser Ser
210 215 220
Leu Gln Glu Ser Gln Leu Arg Cys Glu Gly Ala Leu Glu Leu His Thr
225 230 235 240
His Tyr Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
245 250 255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
260 265 270
His Trp Tyr His Asn Gly Ala Pro Met Glu Ser Asp Glu Gln Ala Gly
275 280 285
Ile Val Leu Ala Glu Asn Leu Ile His Asp Cys Thr Phe Ile Thr Ser
290 295 300
Glu Leu Thr Leu Ser His Ile Gly Val Trp Ala Ser Gly Glu Trp Glu
305 310 315 320
Cys Ser Val Ser Thr Val Gln Gly Asn Thr Ser Lys Lys Val Glu Ile
325 330 335
Val Val Leu Glu Thr Ser Ala Ser Tyr Cys Pro Ala Glu Arg Val Thr
340 345 350
Asn Asn Arg Gly Asp Phe Arg Trp Pro Arg Thr Leu Ala Gly Ile Thr
355 360 365

Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Ser
370 375 380
Gly Gly Ala Pro Gly Thr Arg Ala Ser Arg Arg Cys Asp Arg Ala Gly
385 390 395 400
Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
405 410 415
Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
420 425 430
Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
435 440 445
Ser Phe Ser Asp Met Met Asp Val Val Tyr Val Ala Gln Met Ile Gln
450 455 460
Lys Phe Leu Gly Tyr Val Asp Gln Ile Lys Glu Leu Val Glu Val Met
465 470 475 480
Val Asp Met Ala Ser Asn Leu Met Leu Val Asp Glu His Leu Leu Trp
485 490 495
Leu Ala Gln Arg Glu Asp Lys Ala Cys Ser Gly Ile Val Gly Ala Leu
500 505 510
Glu Arg Ile Gly Gly Ala Ala Leu Ser Pro His Ala Gln His Ile Ser
515 520 525
Val Asn Ser Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
530 535 540
Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Val Gly
545 550 555 560
Val Ser Gly Ala Gln Pro Ser Ser Val Gly Gln Asp Ala Pro Val Glu
565 570 575
Pro Glu Pro Leu Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
580 585 590
Arg Pro Asn Ile Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
595 600 605
Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Thr Leu Pro Ala
610 615 620
Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
625 630 635 640
Phe Arg Asn Gly Arg Leu Phe Arg Ser His Gly Asn Asn Thr Ser Arg
645 650 655
Pro Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val
660 665 670
Ile Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro
675 680 685
Val Ala Val Ser Leu Arg His Trp Ala Glu Gly Ala Asp Pro Met Ala
690 695 700
Ala Trp Trp Asn Gln Asp Gly Pro Gly Gly Trp Ser Ser Glu Gly Cys
705 710 715 720
Arg Leu Arg Tyr Ser Gln Pro Asn Val Ser Ser Leu Tyr Cys Gln His
725 730 735
Leu Gly Asn Val Ala Val Leu Met Glu Leu Asn Ala Phe Pro Arg Glu
740 745 750
Ala Gly Gly Ser Gly Ala Gly Leu His Pro Val Val Tyr Pro Cys Thr
755 760 765
Ala Leu Leu Leu Leu Cys Leu Phe Ser Thr Ile Ile Thr Tyr Ile Leu
770 775 780
Asn His Ser Ser Ile His Val Ser Arg Lys Gly Trp His Met Leu Leu
785 790 795 800
Asn Leu Cys Phe His Met Ala Met Thr Ser Ala Val Phe Val Gly Gly
805 810 815
Val Thr Leu Thr Asn Tyr Gln Met Val Cys Gln Ala Val Gly Ile Thr
820 825 830
Leu His Tyr Ser Ser Leu Ser Ser Leu Leu Trp Met Gly Val Lys Ala
835 840 845
Arg Val Leu His Lys Glu Leu Ser Trp Arg Ala Pro Pro Leu Glu Glu
850 855 860
Gly Glu Ala Ala Pro Pro Gly Pro Arg Pro Met Leu Arg Phe Tyr Leu
865 870 875 880
Ile Ala Gly Gly Ile Pro Leu Ile Ile Cys Gly Ile Thr Ala Ala Val
885 890 895

Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu Val Trp
900 905 910
Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile Leu Pro
915 920 925
Ile Thr Trp Ile Tyr Phe Leu Cys Ala Gly Leu His Leu Arg Ser His
930 935 940
Val Ala Gln Asn Pro Lys Gln Gly Asn Arg Ile Ser Leu Glu Pro Gly
945 950 955 960
Glu Glu Leu Arg Gly Ser Thr Arg Leu Arg Ser Ser Gly Val Leu Leu
965 970 975
Asn Asp Ser Gly Ser Leu Leu Ala Thr Val Ser Ala Gly Val Gly Thr
980 985 990
Pro Ala Pro Pro Glu Asp Gly Asp Gly Val Tyr Ser Pro Gly Val Gln
995 1000 1005
Leu Gly Ala Leu Met Thr Thr His Phe Leu Tyr Leu Ala Met Trp Ala
1010 1015 1020
Cys Gly Ala Leu Ala Val Ser Gln Arg Trp Leu Pro Arg Val Val Cys
1025 1030 1035 1040
Ser Cys Leu Tyr Gly Val Ala Ala Ser Ala Leu Gly Leu Phe Val Phe
1045 1050 1055
Thr His His Cys Ala Arg Arg Arg Asp Val Arg Ala Ser Trp Arg Ala
1060 1065 1070
Cys Cys Pro Pro Ala Ser Pro Ser Ala Ser His Val Pro Ala Arg Ala
1075 1080 1085
Leu Pro Thr Ala Thr Glu Asp Gly Ser Pro Val Leu Gly Glu Gly Pro
1090 1095 1100
Ala Ser Leu Lys Ser Ser Pro Ser Gly Ser Ser Gly Arg Ala Pro Pro
1105 1110 1115 1120
Pro Pro Cys Lys Leu Thr Asn Leu Gln Val Ala Gln Ser Gln Val Cys
1125 1130 1135
Glu Ala Ser Val Ala Ala Arg Gly Asp Gly Glu Pro Glu Pro Thr Gly
1140 1145 1150
Ser Arg Gly Ser Leu Ala Pro Arg His His Asn Asn Leu His His Gly
1155 1160 1165
Arg Arg Val His Lys Ser Arg Ala Lys Gly His Arg Ala Gly Glu Thr
1170 1175 1180
Gly Gly Lys Ser Arg Leu Lys Ala Leu Arg Ala Gly Thr Ser Pro Gly
1185 1190 1195 1200
Ala Pro Glu Leu Leu Ser Ser Glu Ser Gly Ser Leu His Asn Ser Pro
1205 1210 1215
Ser Asp Ser Tyr Pro Gly Ser Ser Arg Asn Ser Pro Gly Asp Gly Leu
1220 1225 1230
Pro Leu Glu Gly Glu Pro Met Leu Thr Pro Ser Glu Gly Ser Asp Thr
1235 1240 1245
Ser Ala Ala Pro Ile Ala Glu Thr Gly Arg Pro Gly Gln Arg Arg Ser
1250 1255 1260
Ala Ser Arg Asp Asn Leu Lys Gly Ser Gly Ser Ala Leu Glu Arg Glu
1265 1270 1275 1280
Ser Lys Arg Arg Ser Tyr Pro Leu Asn Thr Thr Ser Leu Asn Gly Ala
1285 1290 1295
Pro Lys Gly Gly Lys Tyr Glu Asp Ala Ser Val Thr Gly Ala Glu Ala
1300 1305 1310
Ile Ala Gly Gly Ser Met Lys Thr Gly Leu Trp Lys Ser Glu Thr Thr
1315 1320 1325
Val

<210> 192
<211> 500
<212> PRT
<213> Mus musculus

<400> 192
Met Arg Ala Gln Leu Trp Leu Leu Gln Leu Leu Leu Leu Arg Gly Ala
1 5 10 15
Ala Arg Ala Leu Ser Pro Ala Thr Pro Ala Gly His Asn Glu Gly Gln

20 25 30
Asp Ser Ala Trp Thr Ala Lys Arg Thr Arg Gln Gly Trp Ser Arg Arg
35 40 45
Pro Arg Glu Ser Pro Ala Gln Val Leu Lys Pro Gly Lys Thr Gln Leu
50 55 60
Ser Gln Asp Leu Gly Gly Gly Ser Leu Ala Ile Asp Thr Leu Pro Asp
65 70 75 80
Asn Arg Thr Arg Val Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
85 90 95
Val Tyr Gly Pro Gly Glu Lys Gln Ser Gln Asp Leu Trp Val Asp Leu
100 105 110
Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
115 120 125
Ser His Arg Gln Ala Ser Arg Val Val Leu Ser Phe Asp Phe Pro Phe
130 135 140
Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
145 150 155 160
Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
165 170 175
Ala Pro Leu Met Ala Asn Phe Asn Pro Gly Tyr Ser Asp Asn Ser Thr
180 185 190
Val Ala Tyr Phe Asp Asn Gly Thr Val Phe Val Val Gln Trp Asp His
195 200 205
Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala
210 215 220
Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro
225 230 235 240
Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly
245 250 255
Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu
260 265 270
Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
275 280 285
Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
290 295 300
Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
305 310 315 320
Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe
325 330 335
Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala
340 345 350
Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala
355 360 365
Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser
370 375 380
Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu
385 390 395 400
Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
405 410 415
Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
420 425 430
Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
435 440 445
Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
450 455 460
His His Trp Pro Ala Met Lys Phe His Asn His Pro Asn His Ser Thr
465 470 475 480
Tyr Thr Glu Val Glu Pro Ser Gly His Glu Lys Glu Gly Phe Val Glu
485 490 495
Ala Glu Gln Cys
500

<210> 193
<211> 530
<212> PRT
<213> Mus musculus

<400> 193
Met Ala Arg Phe Arg Arg Ala Asp Leu Ala Ala Ala Gly Val Met Leu
1 5 10 15
Leu Cys His Phe Leu Thr Asp Arg Phe His Phe Ala His Gly Glu Pro
20 25 30
Gly His His Thr Asn Asp Trp Ile Tyr Glu Val Thr Asn Ala Phe Pro
35 40 45
Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
50 55 60
Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Met Gly Gln Ala Ser Pro Glu Ser Lys Gly Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
165 170 175
Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205
Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
275 280 285
Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
290 295 300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
305 310 315 320
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Gly Cys Gly Pro
325 330 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
340 345 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
355 360 365
Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys
370 375 380
Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Thr Ser His Thr Thr
385 390 395 400
Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser
405 410 415
Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu
420 425 430
His Leu Lys Asp Ser Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys
435 440 445
Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu
450 455 460
Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His
465 470 475 480
His Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser
485 490 495
Arg Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr
500 505 510

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Gln Cys
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<210> 194
<211> 562
<212> PRT
<213> Mus musculus

<400> 194
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            20                  25                  30
Gly Gly Pro Ala Cys Tyr Gly Gly Phe Asp Leu Tyr Phe Ile Leu Asp
        35                  40                  45
Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
    50                  55                  60
Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
65                  70                  75                  80
Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
                85                  90                  95
Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
            100                 105                 110
Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
        115                 120                 125
Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
    130                 135                 140
Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
145                 150                 155                 160
Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
                165                 170                 175
Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
            180                 185                 190
Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
        195                 200                 205
Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
    210                 215                 220
Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
225                 230                 235                 240
Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
                245                 250                 255
Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
            260                 265                 270
Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
        275                 280                 285
Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser Phe Ile
    290                 295                 300
Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly Ser Ile
305                 310                 315                 320
Leu Ala Ile Ala Leu Leu Val Leu Phe Leu Leu Leu Ala Leu Ala Leu
                325                 330                 335
Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys Glu Val
            340                 345                 350
Pro Pro Pro Pro Val Glu Glu Ser Glu Glu Glu Asp Asp Asp Gly Leu
        355                 360                 365
Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
    370                 375                 380
Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
385                 390                 395                 400
Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
                405                 410                 415
Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
            420                 425                 430
Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
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435 440 445
Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
450 455 460
Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
465 470 475 480
Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
485 490 495
Asn Thr Tyr His Pro Ser Ser Pro Pro Pro Ala Pro Ile Tyr Thr Pro
500 505 510
Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
515 520 525
Pro Pro Ile Pro Ser Pro Pro Ser Thr Leu Pro Pro Pro Pro Gln Ala
530 535 540
Pro Pro Pro Asn Arg Ala Pro Pro Pro Ser Arg Pro Pro Pro Arg Pro
545 550 555 560
Ser Val

<210> 195
<211> 2565
<212> DNA
<213> Homo sapiens

<400> 195
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acccctgggc tgctgagccc cgtgccgcct gcggccccag cagctgctac gctctcttcc
120
cacggcgccg caccttcctg gaggcctggc gggcctgccg cgagctgggg ggcgacctgg
180
ccactcctcg gacccccgag gaggcccagc gtgtggacag cctggtgggt gcgggcccag
240
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360
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420
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480
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600
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660
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720
acgggggctg cgaacacgaa tgtgtggagg aggtggatgg tcacgtgtcc tgccgctgca
780
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840
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900
gtttccggcc agcggaggat gatccgcacc gctgtgtgga cacagatgag tgccagattg
960
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1020
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1080
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1200
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1260

agccacagat accctacccg gagcccacct ggccaccccc gctcagtgcc cccagggtcc
1320
cctaccactc ctcagtgctc tccgtcaccc ggcctgtggt ggtctctgcc acgcatccca
1380
cactgccttc tgcccaccag cctcctgtga tccctgccac acacccagct ttgtcccgtg
1440
accaccagat ccccgtgatc gcagccaact atccagatct gccttctgcc taccaacccg
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1560
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1620
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1680
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1740
ccacccagct tcccattatc ccaactgccc agccctctct gaccaccacc tccaggtccc
1800
ctgtgtctcc tgcccatcaa atctctgtgc ctgctgccac ccagcccgca gccctcccca
1860
ccctcctgcc ctctcagagc ccccactaacc agacctcacc catcagccct acacatcccc
1920
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1980
tgccctcacc agctcccaca gcagccccaa cagccctggg ggaggctggt cttgccgagc
2040
acagccagag ggatgaccgg tggctgctgg tggcactcct ggtgccaacg tgtgtctttt
2100
tggtggtcct gcttgcactg ggcatcgtgt actgcacccg ctgtggcccc catgcaccca
2160
acaagcgcat cactgactgc tatcgctggg tcatccatgc tgggagcaag agcccaacag
2220
aacccatgcc ccccaggggc agcctcacag ggtgcagac ctgcagaacc agcgtgtgat
2280
ggggtgcaga cccccctcat ggagtatggg gcgctggaca catggccggg gctgcaccag
2340
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2400
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2460
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2520
aaatggggtg tcaaccttaa aaaaaaaaaa aaaaaaaaaa aaaaa
2565

<210> 196
<211> 757
<212> PRT
<213> Homo sapiens

<400> 196
Met Leu Leu Arg Leu Leu Leu Ala Trp Ala Ala Ala Gly Pro Thr Leu
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Gly Gln Asp Pro Trp Ala Ala Glu Pro Arg Ala Ala Cys Gly Pro Ser
20 25 30
Ser Cys Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp
35 40 45
Arg Ala Cys Arg Glu Leu Gly Gly Asp Leu Ala Thr Pro Arg Thr Pro
50 55 60
Glu Glu Ala Gln Arg Val Asp Ser Leu Val Gly Ala Gly Pro Ala Ser
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Arg Leu Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Leu
85 90 95
Gln Arg Pro Leu Arg Gly Phe Thr Trp Thr Thr Gly Asp Gln Asp Thr
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Ala Phe Thr Asn Trp Ala Gln Pro Ala Ser Gly Gly Pro Cys Pro Ala

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Gln Arg Cys Val Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu
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Gly Ser Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe
145                 150                 155                 160
Glu Gly Ala Cys Pro Ala Leu Gln Asp Glu Ala Gly Gln Ala Gly Pro
                165                 170                 175
Ala Val Tyr Thr Thr Pro Phe His Leu Val Ser Thr Glu Phe Glu Trp
            180                 185                 190
Leu Pro Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly
        195                 200                 205
Ala Ser Leu Leu Cys Val Lys Gln Pro Glu Gly Gly Val Gly Trp Ser
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Arg Ala Gly Pro Leu Cys Leu Gly Thr Gly Cys Ser Pro Asp Asn Gly
225                 230                 235                 240
Gly Cys Glu His Glu Cys Val Glu Glu Val Asp Gly His Val Ser Cys
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Arg Cys Thr Glu Gly Phe Arg Leu Ala Ala Asp Gly Arg Ser Cys Glu
            260                 265                 270
Asp Pro Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly
        275                 280                 285
Pro Gln Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu
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Asp Asp Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly
305                 310                 315                 320
Val Cys Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr
                325                 330                 335
Cys Ser Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro
            340                 345                 350
Ala Gly Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Gly Asp Glu Leu
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    370                 375                 380
Phe Asn Gly Gly Trp Thr Glu Met Pro Gly Ile Leu Trp Met Glu Pro
385                 390                 395                 400
Thr Gln Pro Pro Asp Phe Ala Leu Ala Tyr Arg Pro Ser Phe Pro Glu
                405                 410                 415
Asp Arg Glu Pro Gln Ile Pro Tyr Pro Glu Pro Thr Trp Pro Pro Pro
            420                 425                 430
Leu Ser Ala Pro Arg Val Pro Tyr His Ser Ser Val Leu Ser Val Thr
        435                 440                 445
Arg Pro Val Val Val Ser Ala Thr His Pro Thr Leu Pro Ser Ala His
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Gln Pro Pro Val Ile Pro Ala Thr His Pro Ala Leu Ser Arg Asp His
465                 470                 475                 480
Gln Ile Pro Val Ile Ala Ala Asn Tyr Pro Asp Leu Pro Ser Ala Tyr
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Gln Pro Gly Ile Leu Ser Val Ser His Ser Ala Gln Pro Pro Ala His
            500                 505                 510
Gln Pro Pro Met Ile Ser Thr Lys Tyr Pro Glu Leu Phe Pro Ala His
        515                 520                 525
Gln Ser Pro Met Phe Pro Asp Thr Arg Val Ala Gly Thr Gln Thr Thr
    530                 535                 540
Thr His Leu Pro Gly Ile Pro Pro Asn His Ala Pro Leu Val Thr Thr
545                 550                 555                 560
Leu Gly Ala Gln Leu Pro Pro Gln Ala Pro Asp Ala Leu Val Leu Arg
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Thr Gln Ala Thr Gln Leu Pro Ile Ile Pro Thr Ala Gln Pro Ser Leu
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Thr Thr Thr Ser Arg Ser Pro Val Ser Pro Ala His Gln Ile Ser Val
        595                 600                 605
Pro Ala Ala Thr Gln Pro Ala Ala Leu Pro Thr Leu Leu Pro Ser Gln
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Ser Pro Thr Asn Gln Thr Ser Pro Ile Ser Pro Thr His Pro His Ser
625                 630                 635                 640
Lys Ala Pro Gln Ile Pro Arg Glu Asp Gly Pro Ser Pro Lys Leu Ala
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Leu Trp Leu Pro Ser Pro Ala Pro Thr Ala Ala Pro Thr Ala Leu Gly
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Glu Ala Gly Leu Ala Glu His Ser Gln Arg Asp Asp Arg Trp Leu Leu
        675                     680                     685
Val Ala Leu Leu Val Pro Thr Cys Val Phe Leu Val Val Leu Leu Ala
    690                     695                     700
Leu Gly Ile Val Tyr Cys Thr Arg Cys Gly Pro His Ala Pro Asn Lys
705                     710                     715                     720
Arg Ile Thr Asp Cys Tyr Arg Trp Val Ile His Ala Gly Ser Lys Ser
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Pro Thr Glu Pro Met Pro Pro Arg Gly Ser Leu Thr Gly Val Gln Thr
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Cys Arg Thr Ser Val
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<213> Homo sapiens

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<211> 266
<212> PRT
<213> Homo sapiens

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Lys Asn Ser Tyr Arg Met Val Val Leu Gly Ala Ser Arg Val Gly Lys

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Thr Pro Thr Ile Glu Asp Phe His Arg Lys Val Tyr Asn Ile Arg Gly
        50                        55                        60
Asp Met Tyr Gln Leu Asp Ile Leu Asp Thr Ser Gly Asn His Pro Phe
65                        70                        75                        80
Pro Ala Met Arg Arg Leu Ser Ile Leu Thr Gly Asp Val Phe Ile Leu
                        85                        90                        95
Val Phe Ser Leu Asp Asn Arg Glu Ser Phe Asp Glu Val Lys Arg Leu
                    100                       105                       110
Gln Lys Gln Ile Leu Glu Val Lys Ser Cys Leu Lys Asn Lys Thr Lys
            115                       120                       125
Glu Ala Ala Glu Leu Pro Met Val Ile Cys Gly Asn Lys Asn Asp His
        130                       135                       140
Gly Glu Leu Cys Arg Gln Val Pro Thr Thr Glu Ala Glu Leu Leu Val
145                       150                       155                       160
Ser Gly Asp Glu Asn Cys Ala Tyr Phe Glu Val Ser Ala Lys Lys Asn
                        165                       170                       175
Thr Asn Val Asp Glu Met Phe Tyr Val Leu Phe Ser Met Ala Lys Leu
                    180                       185                       190
Pro His Glu Met Ser Pro Ala Leu His Arg Lys Ile Ser Val Gln Tyr
            195                       200                       205
Gly Asp Ala Phe His Pro Arg Pro Phe Cys Met Arg Arg Val Lys Glu
        210                       215                       220
Met Asp Ala Tyr Gly Met Val Ser Pro Phe Ala Arg Arg Pro Ser Val
225                       230                       235                       240
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Ala Arg Glu Arg Asp Lys Cys Thr Ile Gln
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<211> 2159
<212> DNA
<213> Homo sapiens

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240
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tctcgaatat atggtccatc tgattctgcc agccgggatt tatgggtgaa catagaccaa
420
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2040
aaaagagcaa tgatgaatgt ctcaagattg ctaagaaaaa cagcccatgc aagagtgaga
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2159

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<211> 529
<212> PRT
<213> Homo sapiens

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Gly Asp Gln Ile Leu Asp Trp Gln Tyr Gly Val Thr Gln Ala Phe Pro
35 40 45
His Thr Glu Glu Glu Val Glu Val Asp Ser His Ala Tyr Ser His Arg
50 55 60
Trp Lys Arg Asn Leu Asp Phe Leu Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Val Gly Gln Asp Ser Pro Glu Pro Arg Ser Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ser Asp Ser Ala Ser

115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Arg Glu Ile Thr
165 170 175
Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205
Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His
275 280 285
Arg Ile Gln Gln Ile Pro Asn Val Arg Arg Arg Thr Ile Tyr Glu Tyr
290 295 300
His Arg Val Glu Leu Gln Met Ser Lys Ile Thr Asn Ile Ser Ala Val
305 310 315 320
Glu Met Thr Pro Leu Pro Thr Cys Leu Gln Phe Asn Arg Cys Gly Pro
325 330 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
340 345 350
Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
355 360 365
Ser Gly Cys Pro Glu Glu Ser Lys Glu Lys Met Cys Glu Asn Thr Glu
370 375 380
Pro Val Glu Thr Ser Ser Arg Thr Thr Thr Thr Ile Gly Ala Thr Thr
385 390 395 400
Thr Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser Gln
405 410 415
Phe Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu His
420 425 430
Leu Lys Asp Asn Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys Lys
435 440 445
Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu Val
450 455 460
Leu Ile Val Ala Thr Ala Ile Leu Val Thr Val Tyr Met Tyr His His
465 470 475 480
Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser Arg
485 490 495
Trp Pro Ala Met Lys Phe Arg Arg Gly Ser Gly His Pro Ala Tyr Ala
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Glu Val Glu Pro Val Gly Glu Lys Glu Gly Phe Ile Val Ser Glu Gln
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Cys

<210> 201
<211> 2608
<212> DNA
<213> Homo sapiens

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180

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2160

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2608

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<211> 350
<212> PRT
<213> Homo sapiens

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Lys Pro Gly Pro Ala Leu Ser Tyr Pro Gln Glu Glu Ala Thr Leu Asn
35 40 45
Glu Met Phe Arg Glu Val Glu Glu Leu Met Glu Asp Thr Gln His Lys
50 55 60
Leu Arg Ser Ala Val Glu Glu Met Glu Ala Glu Glu Ala Ala Ala Lys
65 70 75 80
Ala Ser Ser Glu Val Asn Leu Ala Asn Leu Pro Pro Ser Tyr His Asn
85 90 95
Glu Thr Asn Thr Asp Thr Lys Val Gly Asn Asn Thr Ile His Val His
100 105 110
Arg Glu Ile His Lys Ile Thr Asn Asn Gln Thr Gly Gln Met Val Phe
115 120 125
Ser Glu Thr Val Ile Thr Ser Val Gly Asp Glu Glu Gly Arg Arg Ser
130 135 140
His Glu Cys Ile Ile Asp Glu Asp Cys Gly Pro Ser Met Tyr Cys Gln
145 150 155 160
Phe Ala Ser Phe Gln Tyr Thr Cys Gln Pro Cys Arg Gly Gln Arg Met
165 170 175
Leu Cys Thr Arg Asp Ser Glu Cys Cys Gly Asp Gln Leu Cys Val Trp
180 185 190
Gly His Cys Thr Lys Met Ala Thr Arg Gly Ser Asn Gly Thr Ile Cys
195 200 205
Asp Asn Gln Arg Asp Cys Gln Pro Gly Leu Cys Cys Ala Phe Gln Arg
210 215 220
Gly Leu Leu Phe Pro Val Cys Thr Pro Leu Pro Val Glu Gly Glu Leu
225 230 235 240
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Phe Lys Ser Val Thr Leu Gly Thr Gln Gly Ser Pro Ile Thr Lys Met
1810 1815 1820
Val Ser Val Gly Gly Arg Leu Trp Cys Gly Cys Gln Asn Arg Val Leu
1825 1830 1835 1840
Val Leu Ser Pro Asp Thr Leu Gln Leu Glu His Met Phe Tyr Val Gly
1845 1850 1855
Gln Asp Ser Ser Arg Cys Val Ala Cys Met Val Asp Ser Ser Leu Gly
1860 1865 1870
Val Trp Val Thr Leu Lys Gly Ser Ala His Val Cys Leu Tyr His Pro
1875 1880 1885
Asp Thr Phe Glu Gln Leu Ala Glu Val Asp Val Thr Pro Pro Val His
1890 1895 1900
Arg Met Leu Ala Gly Ser Asp Ala Ile Ile Arg Gln His Lys Ala Ala
1905 1910 1915 1920
Cys Leu Arg Ile Thr Ala Leu Leu Val Cys Glu Glu Leu Leu Trp Val
1925 1930 1935
Gly Thr Ser Ala Gly Val Val Leu Thr Met Pro Thr Ser Pro Gly Thr
1940 1945 1950
Val Ser Cys Pro Arg Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly
1955 1960 1965
His Thr Gly His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly
1970 1975 1980
Phe Asn Leu Leu Cys Pro Thr Pro Pro Pro Pro Pro Asp Thr Gly Pro
1985 1990 1995 2000
Glu Lys Leu Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly
2005 2010 2015
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2020 2025 2030
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Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala
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Thr Gln Glu Ala Pro Arg Pro Ala Ser Ser Leu Arg Pro Pro Arg Cys
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Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr
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115 120 125
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145 150 155 160
Arg Tyr Trp His Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile
165 170 175
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Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp
195 200 205
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His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg
225 230 235 240
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Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly
260 265 270
Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp
275 280 285
Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile
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Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg
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Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp
325 330 335
Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly

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355 360 365
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370 375 380
Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg
385 390 395 400
Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val
405 410 415
Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr
420 425 430
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Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser
50 55 60
Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe
65 70 75 80
Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr
85 90 95
Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe
100 105 110
Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile
115 120 125
Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe
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Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser
145 150 155 160
Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp
165 170 175
Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala
180 185 190
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195 200 205
Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys
210 215 220
Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn
225 230 235 240
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245 250 255
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260 265 270
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Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln
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Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp
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Gly Gly Val Pro Gly Pro Ala Arg Arg Arg Val Val Cys Ser Gly Gly
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Asp Leu Pro Glu Pro Pro Glu Pro Gly Leu Leu Pro Asn Gly Thr Val
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Phe Leu Gly Leu Ser Leu Leu Glu Lys Leu Asp Leu Arg Asn Asn Ile
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Arg Leu Asp Leu Ser Asn Asn Arg Ile Gly Cys Leu Thr Ser Glu Thr
130 135 140
Phe Gln Gly Leu Pro Arg Leu Leu Arg Leu Asn Ile Ser Gly Asn Ile
145 150 155 160
Phe Ser Ser Leu Gln Pro Gly Val Phe Asp Glu Leu Pro Ala Leu Lys
165 170 175
Val Val Asp Leu Gly Thr Glu Phe Leu Thr Cys Asp Cys His Leu Arg
180 185 190
Trp Leu Leu Pro Trp Ala Gln Asn Arg Ser Leu Gln Leu Ser Glu His
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Thr Leu Cys Ala Tyr Pro Ser Ala Leu His Ala Gln Ala Leu Gly Ser
210 215 220
Leu Gln Glu Ala Gln Leu Cys Cys Glu Gly Ala Leu Glu Leu His Thr
225 230 235 240
His His Leu Ile Pro Ser Leu Arg Gln Val Val Phe Gln Gly Asp Arg
245 250 255
Leu Pro Phe Gln Cys Ser Ala Ser Tyr Leu Gly Asn Asp Thr Arg Ile
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Arg Trp Tyr His Asn Arg Ala Pro Val Glu Gly Asp Glu Gln Ala Gly
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Ala Tyr Gln Ser Cys Leu Gln Tyr Pro Phe Thr Ser Val Pro Leu Gly
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Arg Trp Glu Pro Gly Asp Tyr Ser His Cys Leu Tyr Thr Asn Asp Ile
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Thr Arg Val Leu Tyr Thr Phe Val Leu Met Pro Ile Asn Ala Ser Asn
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Ala Leu Thr Leu Ala His Gln Leu Arg Val Tyr Thr Ala Glu Ala Ala
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Val Asn Ala Arg Asn Val Ala Leu Glu Ala Tyr Leu Ile Lys Pro His
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Ser Tyr Val Gly Leu Thr Cys Thr Ala Phe Gln Arg Arg Glu Gly Gly
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Pro Glu Pro Pro Ala Asp Gln Gln Leu Arg Phe Arg Cys Thr Thr Gly
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Arg Pro Asn Val Ser Leu Ser Ser Phe His Ile Lys Asn Ser Val Ala
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Leu Ala Ser Ile Gln Leu Pro Pro Ser Leu Phe Ser Ser Leu Pro Ala
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Ala Leu Ala Pro Pro Val Pro Pro Asp Cys Thr Leu Gln Leu Leu Val
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Phe Arg Asn Gly Arg Leu Phe His Ser His Ser Asn Thr Ser Arg Pro
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Gly Ala Ala Gly Pro Gly Lys Arg Arg Gly Val Ala Thr Pro Val Ile
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Phe Ala Gly Thr Ser Gly Cys Gly Val Gly Asn Leu Thr Glu Pro Val
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Gly Cys Gln Leu Arg Ser Ser Gln Pro Asn Val Ser Ala Leu His Cys
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Gln His Leu Gly Asn Val Ala Val Leu Met Glu Leu Ser Ala Phe Pro
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Arg Glu Val Gly Gly Ala Gly Ala Gly Leu His Pro Val Val Tyr Pro
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Cys Thr Ala Leu Leu Leu Leu Cys Leu Phe Ala Thr Ile Ile Thr Tyr
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Ile Leu Asn His Ser Ser Ile Arg Val Ser Arg Lys Gly Trp His Met
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Gln Glu Gly Asp Pro Ala Leu Pro Thr Pro Ser Pro Met Leu Arg Phe
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Ala Val Asn Ile His Asn Tyr Arg Asp His Ser Pro Tyr Cys Trp Leu
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Val Trp Arg Pro Ser Leu Gly Ala Phe Tyr Ile Pro Val Ala Leu Ile
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<211> 161
<212> PRT
<213> Homo sapiens

<400> 220
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Ser Arg Gly Gln Lys Val Thr Ser Leu Thr Ala Cys Leu Val Asp Gln
20 25 30
Ser Leu Arg Leu Asp Cys Arg His Glu Asn Thr Ser Ser Ser Pro Ile
35 40 45
Gln Tyr Glu Phe Ser Leu Thr Arg Glu Thr Lys Lys His Val Leu Phe
50 55 60
Gly Thr Val Gly Val Pro Glu His Thr Tyr Arg Ser Arg Thr Asn Phe
65 70 75 80
Thr Ser Lys Tyr His Met Lys Val Leu Tyr Leu Ser Ala Phe Thr Ser
85 90 95
Lys Asp Glu Gly Thr Tyr Thr Cys Ala Leu His His Ser Gly His Ser

100 105 110
Pro Pro Ile Ser Ser Gln Asn Val Thr Val Leu Arg Asp Lys Leu Val
115 120 125
Lys Cys Glu Gly Ile Ser Leu Leu Ala Gln Asn Thr Ser Trp Leu Leu
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Leu Leu Leu Leu Ser Leu Ser Leu Leu Gln Ala Thr Asp Phe Met Ser
145 150 155 160
Leu

<210> 221
<211> 736
<212> DNA
<213> Homo sapiens

<400> 221
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360
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736

<210> 222
<211> 594
<212> DNA
<213> Homo sapiens

<400> 222
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240
ggccaccaaa gatgactact acagacgtcc gctgcgggta ctaagagcca ggcaacagac
300
cgttgggggg gtgaattact tcttcgacgt agaggtgggc cgaaccatat gtaccaagtc
360
ccagcccaac ttggacacct gtgccttcca tgaacagcca gaactgcaga agaaacagtt
420
gtgctctttc gagatctacg aagttccctg ggagaacaga aggtccctgg tgaaatccag
480

gtgtcaagaa tcctagggat ctgtgccagg ccattcgcac cagccaccac ccactcccac
540
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<210> 223
<211> 141
<212> PRT
<213> Homo sapiens

<400> 223
Met Ala Arg Pro Leu Cys Thr Leu Leu Leu Leu Met Ala Thr Leu Ala
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Gly Ala Leu Ala Ser Ser Ser Lys Glu Glu Asn Arg Ile Ile Pro Gly
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Gly Ile Tyr Asp Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
35 40 45
His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Glu Asp Glu Tyr Tyr
50 55 60
Arg Arg Pro Leu Gln Val Leu Arg Ala Arg Glu Gln Thr Phe Gly Gly
65 70 75 80
Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
85 90 95
Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
100 105 110
Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
115 120 125
Asp Arg Met Ser Leu Val Asn Ser Arg Cys Gln Glu Ala
130 135 140

<210> 224
<211> 141
<212> PRT
<213> Homo sapiens

<400> 224
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20 25 30
Gly Ile Tyr Asn Ala Asp Leu Asn Asp Glu Trp Val Gln Arg Ala Leu
35 40 45
His Phe Ala Ile Ser Glu Tyr Asn Lys Ala Thr Lys Asp Asp Tyr Tyr
50 55 60
Arg Arg Pro Leu Arg Val Leu Arg Ala Arg Gln Gln Thr Val Gly Gly
65 70 75 80
Val Asn Tyr Phe Phe Asp Val Glu Val Gly Arg Thr Ile Cys Thr Lys
85 90 95
Ser Gln Pro Asn Leu Asp Thr Cys Ala Phe His Glu Gln Pro Glu Leu
100 105 110
Gln Lys Lys Gln Leu Cys Ser Phe Glu Ile Tyr Glu Val Pro Trp Glu
115 120 125
Asn Arg Arg Ser Leu Val Lys Ser Arg Cys Gln Glu Ser
130 135 140

<210> 225
<211> 5460
<212> DNA
<213> Homo sapiens

<400> 225
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120

aaggggagct ggctacttct cgctctgctt catcccacta ttattttggc acaacaggaa
180
gctgttgaag gaggatgttc ccatcttggt cagtcctatg cggatagaga tgtctggaag
240
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300
tgtgacgatc aagaattaga ctgccccaac ccagaaattc catttggaga atgttgtgca
360
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420
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480
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660
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720
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780
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1140
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1200
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1380
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<210> 226
<211> 1466
<212> PRT
<213> Homo sapiens

<400> 226
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20 25 30
Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu
35 40 45
Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp
50 55 60
Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro
65 70 75 80

Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr
85 90 95

Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly
100 105 110

Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln
115 120 125

Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys
130 135 140

Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val
145 150 155 160

Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala
165 170 175

Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly
180 185 190

Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln
195 200 205

Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser
210 215 220

Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly
225 230 235 240

Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile
245 250 255

Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn
260 265 270

Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly
275 280 285

Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala
290 295 300

Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg
305 310 315 320

Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly
325 330 335

Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu
340 345 350

Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg
355 360 365

Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly
370 375 380

Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro
385 390 395 400

Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro
405 410 415

Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly
420 425 430

Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu
435 440 445

Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp
450 455 460

Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly
465 470 475 480

Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro
485 490 495

Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro
500 505 510

Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly
515 520 525

Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly
530 535 540

Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser
545 550 555 560

Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly
565 570 575

Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys
580 585 590

Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro
595 600 605

Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly
610 615 620
Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu
625 630 635 640
Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro
645 650 655
Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly
660 665 670
Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu
675 680 685
Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu
690 695 700
Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly
705 710 715 720
Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser
725 730 735
Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp
740 745 750
Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly
755 760 765
Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala
770 775 780
Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg
785 790 795 800
Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly
805 810 815
Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu
820 825 830
Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser
835 840 845
Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly
850 855 860
Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu
865 870 875 880
Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser
885 890 895
Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly
900 905 910
Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln
915 920 925
Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro
930 935 940
Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly
945 950 955 960
Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val
965 970 975
Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg
980 985 990
Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly
995 1000 1005
Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg
1010 1015 1020
Asp Gly Ser Pro Gly Gly Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro
1025 1030 1035 1040
Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly
1045 1050 1055
Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro
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Ala Gly Ala Pro Gly Pro Ala Gly Ser Arg Gly Ala Pro Gly Pro Gln
1075 1080 1085
Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly
1090 1095 1100
Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser
1105 1110 1115 1120
Pro Gly Pro Ala Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala
1125 1130 1135

Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly
1140 1145 1150
Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn
1155 1160 1165
Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro
1170 1175 1180
Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val
1185 1190 1195 1200
Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe
1205 1210 1215
Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp
1220 1225 1230
Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu
1235 1240 1245
Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp
1250 1255 1260
Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp
1265 1270 1275 1280
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Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe
1315 1320 1325
Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu
1330 1335 1340
Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu
1345 1350 1355 1360
Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile
1365 1370 1375
Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu
1380 1385 1390
Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe
1395 1400 1405
Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp
1410 1415 1420
Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro
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Gly Val Asp Val Gly Pro Val Cys Phe Leu
1460 1465

<210> 227
<211> 6663
<212> DNA
<213> Homo sapiens

<400> 227
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Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly
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Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
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Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
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Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
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Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
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Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
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Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly
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Thr Tyr Ile Gln Lys Leu Gln Ser Phe Leu Asp Pro Ser Val Thr Arg
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Phe Ala Gln Cys Ser Val Met Phe Asp Phe Glu Gly Leu Glu Ser Gly
145 150 155 160
Asp Asp Gly Ala Phe Asp Lys Leu Arg Ser Trp Ser Arg Ser Ile Glu
165 170 175
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180 185 190
Ala Arg Ser Ala Arg Gln Ser Val Leu Arg Tyr Ser Thr Leu Pro Gly
195 200 205
Arg Arg Ala Leu Lys Asn Ser Arg Leu Val Ser Gln Lys Asp Asp Val
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Phe Asn Leu Val Met Ser His Pro His Ala Val Asn Glu Ile Ala Leu
245 250 255
Ser Leu Asn Asn Lys Asn Pro Arg Thr Lys Ala Leu Val Leu Glu Leu
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275 280 285
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Lys Leu Met Glu Tyr Phe Arg Asn Glu Asp Ser Asn Ile Asp Phe Met
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Val Ala Cys Met Gln Phe Ile Asn Ile Val Val His Ser Val Glu Asp
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385 390 395 400
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Arg Glu Lys Glu Leu Glu Ser Ile Lys Glu Thr Tyr Glu Asn Thr Ser
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Val Asp Ser Glu Ala Leu Ala Arg Val Gly Pro Ala Glu Leu Ser Glu
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Gly Met Pro Pro Ser Asp Leu Asp Leu Leu Ala Pro Ala Pro Pro Pro
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Glu Glu Val Leu Pro Leu Pro Pro Pro Pro Ala Pro Pro Leu Pro Pro
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Gly Ala Ala Pro Ser Val Val Leu Thr Val Gly Leu Ser Ala Ile Arg

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Ala Glu Val Lys Leu Leu Arg Gln Tyr Glu Arg Glu Arg Gln Pro Leu
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Glu Arg Leu Thr Gln Arg Met Ala Gly Met Ala Phe Leu Gly Asn Phe
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Gln Asp Asn Leu Gln Met Leu Thr Pro Gln Leu Asn Ala Ile Ile Ala
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Val Tyr Gly Phe Lys Leu Gln Ser Leu Asp Leu Leu Leu Asp Thr Lys
785                 790                 795                 800
Ser Thr Asp Arg Lys Met Thr Leu Leu His Phe Ile Ala Leu Thr Val
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Lys Glu Lys Tyr Pro Asp Leu Ala Asn Phe Trp His Glu Leu His Phe
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Val Glu Lys Ala Ala Ala Val Ser Leu Glu Asn Val Leu Leu Asp Val
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His Asp Asn Ser Val Leu Arg Asn Phe Leu Ser Thr Asn Glu Gly Lys
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Leu Asp Lys Leu Gln Arg Asp Ala Lys Thr Ala Glu Glu Ala Tyr Asn
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Ser Thr Leu Ser Lys Ser Arg Pro Thr Pro Lys Pro Arg Gln Arg Pro
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Gly Ser Pro Leu Val Gly Gln Pro Lys Asn Arg Thr Gly Asp Val Tyr
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His Met Glu Gly Lys Glu Thr Val Cys Ile Asn Ala Thr Val Cys Phe

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Gln Tyr Arg Val Thr Leu Asp Ser Leu Arg Gln Ile Ser Arg Ser Phe

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Phe Ser Gly Thr Gln Glu Arg Lys Val Gln Arg Asn Ile Thr Val Arg

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Lys Ser Glu Cys Thr Lys His Ser Phe Tyr Met Leu Asp Lys His Asp

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agaggcttca ctggaaaaga cagtgcaatg ggacccaggg gcccaccagg gcggccggga
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8640
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cagaacatga tgcgagcagt tgcaagacaa gtctgtgaac aattgataag tggtcagatg
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aacagattca atcagatgct gaatcagatt ccaaatgatt accagtccag tcgcaaccag
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9060
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<212> PRT
<213> Homo sapiens

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Phe Lys Ile Ile Asp Glu Asn Thr Val His Met Ser Trp Ala Glu Pro
        35                  40                  45
Val Asp Pro Ile Val Gly Tyr Arg Ile Thr Val Asp Pro Thr Thr Asp
    50                  55                  60
Gly Pro Thr Lys Glu Phe Thr Leu Ser Ala Ser Thr Thr Glu Thr Leu
65                  70                  75                  80
Leu Ser Glu Leu Val Pro Glu Thr Glu Tyr Val Val Thr Ile Thr Ser
                85                  90                  95
Tyr Asp Glu Val Glu Glu Ser Val Pro Val Ile Gly Gln Leu Thr Ile
            100                 105                 110
Gln Thr Gly Ser Ser Thr Lys Pro Val Glu Lys Lys Pro Gly Lys Thr
        115                 120                 125
Glu Ile Gln Lys Cys Ser Val Ser Ala Trp Thr Asp Leu Val Phe Leu
    130                 135                 140
Val Asp Gly Ser Trp Ser Val Gly Arg Asn Asn Phe Lys Tyr Ile Leu
145                 150                 155                 160
Asp Phe Ile Ala Ala Leu Val Ser Ala Phe Asp Ile Gly Glu Glu Lys
                165                 170                 175
Thr Arg Val Gly Val Val Gln Tyr Ser Ser Asp Thr Arg Thr Glu Phe
            180                 185                 190
Asn Leu Asn Gln Tyr Tyr Gln Arg Asp Glu Leu Leu Ala Ala Ile Lys
        195                 200                 205
Lys Ile Pro Tyr Lys Gly Gly Asn Thr Met Thr Gly Asp Ala Ile Asp
    210                 215                 220
Tyr Leu Val Lys Asn Thr Phe Thr Glu Ser Ala Gly Ala Arg Val Gly
225                 230                 235                 240
Phe Pro Lys Val Ala Ile Ile Ile Thr Asp Gly Lys Ser Gln Asp Glu
                245                 250                 255
Val Glu Ile Pro Ala Arg Glu Leu Arg Asn Val Gly Val Glu Val Phe
            260                 265                 270
Ser Leu Gly Ile Lys Ala Ala Asp Ala Lys Glu Leu Lys Gln Ile Ala
        275                 280                 285
Ser Thr Pro Ser Leu Asn His Val Phe Asn Val Ala Asn Phe Asp Ala
    290                 295                 300
Ile Val Asp Ile Gln Asn Glu Ile Ile Ser Gln Val Cys Ser Gly Val
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Asp Glu Gln Leu Gly Glu Leu Val Ser Gly Glu Glu Val Val Glu Pro
                325                 330                 335
Pro Ser Asn Leu Ile Ala Met Glu Val Ser Ser Lys Tyr Val Lys Leu
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Asn Trp Asn Pro Ser Pro Ser Pro Val Thr Gly Tyr Lys Val Ile Leu
        355                 360                 365
Thr Pro Met Thr Ala Gly Ser Arg Gln His Ala Leu Ser Val Gly Pro
    370                 375                 380
Gln Thr Thr Thr Leu Ser Val Arg Asp Leu Ser Ala Asp Thr Glu Tyr
385                 390                 395                 400
Gln Ile Ser Val Ser Ala Met Lys Gly Met Thr Ser Ser Glu Pro Ile
                405                 410                 415
Ser Ile Met Glu Lys Thr Gln Pro Met Lys Val Gln Val Glu Cys Ser
            420                 425                 430
Arg Gly Val Asp Ile Lys Ala Asp Ile Val Phe Leu Val Asp Gly Ser
        435                 440                 445
Tyr Ser Ile Gly Ile Ala Asn Phe Val Lys Val Arg Ala Phe Leu Glu
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Val Leu Val Lys Ser Phe Glu Ile Ser Pro Asn Arg Val Gln Ile Ser
465                 470                 475                 480
Leu Val Gln Tyr Ser Arg Asp Pro His Thr Glu Phe Thr Leu Lys Lys
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Phe Thr Lys Val Glu Asp Ile Ile Glu Ala Ile Asn Thr Phe Pro Tyr
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Arg Gly Gly Ser Thr Asn Thr Gly Lys Ala Met Thr Tyr Val Arg Glu
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Lys Ile Phe Val Pro Ser Lys Gly Ser Arg Ser Asn Val Pro Lys Val
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Met Ile Leu Ile Thr Asp Gly Lys Ser Ser Asp Ala Phe Arg Asp Pro
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Lys Asp Ala Val Arg Ser Glu Leu Glu Ala Ile Ala Ser Pro Pro Ala
            580                     585                 590
Glu Thr His Val Phe Thr Val Glu Asp Phe Asp Ala Phe Gln Arg Ile
        595                     600                 605
Ser Phe Glu Leu Thr Gln Ser Ile Cys Leu Arg Ile Glu Gln Glu Leu
    610                     615                 620
Ala Ala Ile Lys Lys Lys Ala Tyr Val Pro Pro Lys Asp Leu Ser Phe
625                 630                     635                 640
Ser Glu Val Thr Ser Tyr Gly Phe Lys Thr Asn Trp Ser Pro Ala Gly
                645                     650                 655
Glu Asn Val Phe Ser Tyr His Ile Thr Tyr Lys Glu Ala Ala Gly Asp
            660                     665                 670
Asp Glu Val Thr Val Val Glu Pro Ala Ser Ser Thr Ser Val Val Leu
        675                     680                 685
Ser Ser Leu Lys Pro Glu Thr Leu Tyr Leu Val Asn Val Thr Ala Glu
    690                     695                 700
Tyr Glu Asp Gly Phe Ser Ile Pro Leu Ala Gly Glu Glu Thr Thr Glu
705                 710                     715                 720
Glu Val Lys Gly Ala Pro Arg Asn Leu Lys Val Thr Asp Glu Thr Thr
                725                     730                 735
Asp Ser Phe Lys Ile Thr Trp Thr Gln Ala Pro Gly Arg Val Leu Arg
            740                     745                 750
Cys Arg Ile Ile Tyr Arg Pro Val Ala Gly Gly Glu Ser Arg Glu Val
        755                     760                 765
Thr Thr Pro Pro Asn Gln Arg Arg Arg Thr Leu Glu Asn Leu Ile Pro
    770                     775                 780
Asp Thr Lys Tyr Glu Val Ser Val Ile Pro Glu Tyr Phe Ser Gly Pro
785                 790                     795                 800
Gly Thr Pro Leu Thr Gly Asn Ala Ala Thr Glu Glu Val Arg Gly Asn
                805                     810                 815
Pro Arg Asp Leu Arg Val Ser Asp Pro Thr Thr Ser Thr Met Lys Leu
            820                     825                 830
Ser Trp Ser Gly Ala Pro Gly Lys Val Lys Gln Tyr Leu Val Thr Tyr
        835                     840                 845
Thr Pro Val Ala Gly Gly Glu Thr Gln Glu Val Thr Val Arg Gly Asp
    850                     855                 860
Thr Thr Asn Thr Val Leu Gln Gly Leu Lys Glu Gly Thr Gln Tyr Ala
865                 870                     875                 880
Leu Ser Val Thr Ala Leu Tyr Ala Ser Gly Ala Gly Asp Ala Leu Phe
                885                     890                 895
Gly Glu Gly Thr Thr Leu Glu Glu Arg Gly Ser Pro Gln Asp Leu Val
            900                     905                 910
Thr Lys Asp Ile Thr Asp Thr Ser Ile Gly Ala Tyr Trp Thr Ser Ala
        915                     920                 925
Pro Gly Met Val Arg Gly Tyr Arg Val Ser Trp Lys Ser Leu Tyr Asp
    930                     935                 940
Asp Val Asp Thr Gly Glu Lys Asn Leu Pro Glu Asp Ala Ile His Thr
945                 950                     955                 960
Met Ile Glu Asn Leu Gln Pro Glu Thr Lys Tyr Arg Ile Ser Val Phe
                965                     970                 975
Ala Thr Tyr Ser Ser Gly Glu Gly Glu Pro Leu Thr Gly Asp Ala Thr
            980                     985                 990
Thr Glu Leu Ser Gln Asp Ser Lys Thr Leu Lys Val Asp Glu Glu Thr
        995                     1000                1005
Glu Asn Thr Met Arg Val Thr Trp Lys Pro Ala Pro Gly Lys Val Val
    1010                    1015                1020
Asn Tyr Arg Val Val Tyr Arg Pro His Gly Arg Gly Lys Gln Met Val
1025                1030                    1035                1040
Ala Lys Val Pro Pro Thr Val Thr Ser Thr Val Leu Lys Arg Leu Gln
                1045                    1050                1055
Pro Gln Thr Thr Tyr Asp Ile Thr Val Leu Pro Ile Tyr Lys Met Gly
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Glu Gly Lys Leu Arg Gln Gly Ser Gly Thr Thr Ala Ser Arg Phe Lys
1075 1080 1085
Ser Pro Arg Asn Leu Lys Thr Ser Asp Pro Thr Met Ser Ser Phe Arg
1090 1095 1100
Val Thr Trp Glu Pro Ala Pro Gly Glu Val Lys Gly Tyr Lys Val Thr
1105 1110 1115 1120
Phe His Pro Thr Gly Asp Asp Arg Arg Leu Gly Glu Leu Val Val Gly
1125 1130 1135
Pro Tyr Asp Asn Thr Val Val Leu Glu Glu Leu Arg Ala Gly Thr Thr
1140 1145 1150
Tyr Lys Val Asn Val Phe Gly Met Phe Asp Gly Gly Glu Ser Ser Pro
1155 1160 1165
Leu Val Gly Gln Glu Met Thr Thr Leu Ser Asp Thr Thr Val Met Pro
1170 1175 1180
Ile Leu Ser Ser Gly Met Glu Cys Leu Thr Arg Ala Glu Ala Asp Ile
1185 1190 1195 1200
Val Leu Leu Val Asp Gly Ser Trp Ser Ile Gly Arg Ala Asn Phe Arg
1205 1210 1215
Thr Val Arg Ser Phe Ile Ser Arg Ile Val Glu Val Phe Asp Ile Gly
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Pro Lys Arg Val Gln Ile Ala Leu Ala Gln Tyr Ser Gly Asp Pro Arg
1235 1240 1245
Thr Glu Trp Gln Leu Asn Ala His Arg Asp Lys Lys Ser Leu Leu Gln
1250 1255 1260
Ala Val Ala Asn Leu Pro Tyr Lys Gly Gly Asn Thr Leu Thr Gly Met
1265 1270 1275 1280
Ala Leu Asn Phe Ile Arg Gln Gln Asn Phe Arg Thr Gln Ala Gly Met
1285 1290 1295
Arg Pro Arg Ala Arg Lys Ile Gly Val Leu Ile Thr Asp Gly Lys Ser
1300 1305 1310
Gln Asp Asp Val Glu Ala Pro Ser Lys Lys Leu Lys Asp Glu Gly Val
1315 1320 1325
Glu Leu Phe Ala Ile Gly Ile Lys Asn Ala Asp Glu Val Glu Leu Lys
1330 1335 1340
Met Ile Ala Thr Asp Pro Asp Asp Thr His Asp Tyr Asn Val Ala Asp
1345 1350 1355 1360
Phe Glu Ser Leu Ser Arg Ile Val Asp Asp Leu Thr Ile Asn Leu Cys
1365 1370 1375
Asn Ser Val Lys Gly Pro Gly Asp Leu Glu Ala Pro Ser Asn Leu Val
1380 1385 1390
Ile Ser Glu Arg Thr His Arg Ser Phe Arg Val Ser Trp Thr Pro Pro
1395 1400 1405
Ser Asp Ser Val Asp Arg Tyr Lys Val Glu Tyr Tyr Pro Val Ser Gly
1410 1415 1420
Gly Lys Arg Gln Glu Phe Tyr Val Ser Arg Met Glu Thr Ser Thr Val
1425 1430 1435 1440
Leu Lys Asp Leu Lys Pro Glu Thr Glu Tyr Val Val Asn Val Tyr Ser
1445 1450 1455
Val Val Glu Asp Glu Tyr Ser Glu Pro Leu Lys Gly Thr Glu Lys Thr
1460 1465 1470
Leu Pro Val Pro Val Val Ser Leu Asn Ile Tyr Asp Val Gly Pro Thr
1475 1480 1485
Thr Met His Val Gln Trp Gln Pro Val Gly Gly Ala Thr Gly Tyr Ile
1490 1495 1500
Leu Ser Tyr Lys Pro Val Lys Asp Thr Glu Pro Thr Arg Pro Lys Glu
1505 1510 1515 1520
Val Arg Leu Gly Pro Thr Val Asn Asp Met Gln Leu Thr Asp Leu Val
1525 1530 1535
Pro Asn Thr Glu Tyr Ala Val Thr Val Gln Ala Val Leu His Asp Leu
1540 1545 1550
Thr Ser Glu Pro Val Thr Val Arg Glu Val Thr Leu Pro Leu Pro Arg
1555 1560 1565
Pro Gln Asp Leu Lys Leu Arg Asp Val Thr His Ser Thr Met Asn Val
1570 1575 1580
Phe Trp Glu Pro Val Pro Gly Lys Val Arg Lys Tyr Ile Val Arg Tyr

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Lys Thr Pro Glu Glu Asp Val Lys Glu Val Glu Val Asp Arg Ser Glu
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Thr Ser Thr Ser Leu Lys Asp Leu Phe Ser Gln Thr Leu Tyr Thr Val
            1620                1625                1630
Ser Val Ser Ala Val His Asp Glu Gly Glu Ser Pro Pro Val Thr Ala
        1635                1640                1645
Gln Glu Thr Thr Arg Pro Val Pro Ala Pro Thr Asn Leu Lys Ile Thr
    1650                1655                1660
Glu Val Thr Ser Glu Gly Phe Arg Gly Thr Trp Asp His Gly Ala Ser
1665                1670                1675                1680
Asp Val Ser Leu Tyr Arg Ile Thr Trp Gly Pro Phe Gly Ser Ser Asp
                1685                1690                1695
Lys Met Glu Thr Ile Leu Asn Gly Asp Glu Asn Thr Leu Val Phe Glu
            1700                1705                1710
Asn Leu Asn Pro Asn Thr Ile Tyr Glu Val Ser Ile Thr Ala Ile Tyr
        1715                1720                1725
Ala Asp Glu Ser Glu Ser Asp Asp Leu Ile Gly Ser Glu Arg Thr Leu
    1730                1735                1740
Pro Ile Leu Thr Thr Gln Ala Pro Lys Ser Gly Pro Arg Asn Leu Gln
1745                1750                1755                1760
Val Tyr Asn Ala Thr Ser Asn Ser Leu Thr Val Lys Trp Asp Pro Ala
                1765                1770                1775
Ser Gly Arg Val Gln Lys Tyr Arg Ile Thr Tyr Gln Pro Ser Thr Gly
            1780                1785                1790
Glu Gly Asn Glu Gln Thr Thr Thr Ile Gly Gly Arg Gln Asn Ser Val
        1795                1800                1805
Val Leu Gln Lys Leu Lys Pro Asp Thr Pro Tyr Thr Ile Thr Val Ser
    1810                1815                1820
Ser Leu Tyr Pro Asp Gly Glu Gly Gly Arg Met Thr Gly Arg Gly Lys
1825                1830                1835                1840
Thr Lys Pro Leu Asn Thr Val Arg Asn Leu Arg Val Tyr Asp Pro Ser
                1845                1850                1855
Thr Ser Thr Leu Asn Val Arg Trp Asp His Ala Glu Gly Asn Pro Arg
            1860                1865                1870
Gln Tyr Lys Leu Phe Tyr Ala Pro Ala Ala Gly Gly Pro Glu Glu Leu
        1875                1880                1885
Val Pro Ile Pro Gly Asn Thr Asn Tyr Ala Ile Leu Arg Asn Leu Gln
    1890                1895                1900
Pro Asp Thr Ser Tyr Thr Val Thr Val Val Pro Val Tyr Thr Glu Gly
1905                1910                1915                1920
Asp Gly Gly Arg Thr Ser Asp Thr Gly Arg Thr Leu Met Arg Gly Leu
                1925                1930                1935
Ala Arg Asn Val Gln Val Tyr Asn Pro Thr Pro Asn Arg Leu Gly Val
            1940                1945                1950
Arg Trp Asp Pro Ala Pro Gly Pro Val Leu Gln Tyr Arg Val Val Tyr
        1955                1960                1965
Ser Pro Val Asp Gly Thr Arg Pro Ser Glu Ser Ile Val Val Pro Gly
    1970                1975                1980
Asn Thr Arg Met Val His Leu Glu Arg Leu Ile Pro Asp Thr Leu Tyr
1985                1990                1995                2000
Ser Val Asn Leu Val Ala Leu Tyr Ser Asp Gly Glu Gly Asn Pro Ser
                2005                2010                2015
Pro Ala Gln Gly Arg Thr Leu Pro Arg Ser Gly Pro Arg Asn Leu Arg
            2020                2025                2030
Val Phe Gly Glu Thr Thr Asn Ser Leu Ser Val Ala Trp Asp His Ala
        2035                2040                2045
Asp Gly Pro Val Gln Gln Tyr Arg Ile Ile Tyr Ser Pro Thr Val Gly
    2050                2055                2060
Asp Pro Ile Asp Glu Tyr Thr Thr Val Pro Gly Arg Arg Asn Asn Val
2065                2070                2075                2080
Ile Leu Gln Pro Leu Gln Pro Asp Thr Pro Tyr Lys Ile Thr Val Ile
                2085                2090                2095
Ala Val Tyr Glu Asp Gly Asp Gly Gly His Leu Thr Gly Asn Gly Arg
            2100                2105                2110
Thr Val Gly Leu Leu Pro Pro Gln Asn Ile His Ile Ser Asp Glu Trp
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        2115                2120                2125
Tyr Thr Arg Phe Arg Val Ser Trp Asp Pro Ser Pro Ser Pro Val Leu
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Gly Tyr Lys Ile Val Tyr Lys Pro Val Gly Ser Asn Glu Pro Met Glu
2145                2150                2155                2160
Ala Phe Val Gly Glu Met Thr Ser Tyr Thr Leu His Asn Leu Asn Pro
                2165                2170                2175
Ser Thr Thr Tyr Asp Val Asn Val Tyr Ala Gln Tyr Asp Ser Gly Leu
            2180                2185                2190
Ser Val Pro Leu Thr Asp Gln Gly Thr Thr Leu Tyr Leu Asn Val Thr
        2195                2200                2205
Asp Leu Lys Thr Tyr Gln Ile Gly Trp Asp Thr Phe Cys Val Lys Trp
    2210                2215                2220
Ser Pro His Arg Ala Ala Thr Ser Tyr Arg Leu Lys Leu Ser Pro Ala
2225                2230                2235                2240
Asp Gly Thr Arg Gly Gln Glu Ile Thr Val Arg Gly Ser Glu Thr Ser
                2245                2250                2255
His Cys Phe Thr Gly Leu Ser Pro Asp Thr Asp Tyr Gly Val Thr Val
            2260                2265                2270
Phe Val Gln Thr Pro Asn Leu Glu Gly Pro Gly Val Ser Val Lys Glu
        2275                2280                2285
His Thr Thr Val Lys Pro Thr Glu Ala Pro Thr Glu Pro Pro Thr Pro
    2290                2295                2300
Pro Pro Pro Pro Thr Ile Pro Pro Ala Arg Asp Val Cys Lys Gly Ala
2305                2310                2315                2320
Lys Ala Asp Ile Val Phe Leu Thr Asp Ala Ser Trp Ser Ile Gly Asp
                2325                2330                2335
Asp Asn Phe Asn Lys Val Val Lys Phe Ile Phe Asn Thr Val Gly Gly
            2340                2345                2350
Phe Asp Glu Ile Ser Pro Ala Gly Ile Gln Val Ser Phe Val Gln Tyr
        2355                2360                2365
Ser Asp Glu Val Lys Ser Glu Phe Lys Leu Asn Thr Tyr Asn Asp Lys
    2370                2375                2380
Ala Leu Ala Leu Gly Ala Leu Gln Asn Ile Arg Tyr Arg Gly Gly Asn
2385                2390                2395                2400
Thr Arg Thr Gly Lys Ala Leu Thr Phe Ile Lys Glu Lys Val Leu Thr
                2405                2410                2415
Trp Glu Ser Gly Met Arg Lys Asn Val Pro Lys Val Leu Val Val Val
            2420                2425                2430
Thr Asp Gly Arg Ser Gln Asp Glu Val Lys Lys Ala Ala Leu Val Ile
        2435                2440                2445
Gln Gln Ser Gly Phe Ser Val Phe Val Val Gly Val Ala Asp Val Asp
    2450                2455                2460
Tyr Asn Glu Leu Ala Asn Ile Ala Ser Lys Pro Ser Glu Arg His Val
2465                2470                2475                2480
Phe Ile Val Asp Asp Phe Glu Ser Phe Glu Lys Ile Glu Asp Asn Leu
                2485                2490                2495
Ile Thr Phe Val Cys Glu Thr Ala Thr Ser Ser Cys Pro Leu Ile Tyr
            2500                2505                2510
Leu Asp Gly Tyr Thr Ser Pro Gly Phe Lys Met Leu Glu Ala Tyr Asn
        2515                2520                2525
Leu Thr Glu Lys Asn Phe Ala Ser Val Gln Gly Val Ser Leu Glu Ser
    2530                2535                2540
Gly Ser Phe Pro Ser Tyr Ser Ala Tyr Arg Ile Gln Lys Asn Ala Phe
2545                2550                2555                2560
Val Asn Gln Pro Thr Ala Asp Leu His Pro Asn Gly Leu Pro Pro Ser
                2565                2570                2575
Tyr Thr Ile Ile Leu Leu Phe Arg Leu Leu Pro Glu Thr Pro Ser Asp
            2580                2585                2590
Pro Phe Ala Ile Trp Gln Ile Thr Asp Arg Asp Tyr Lys Pro Gln Val
        2595                2600                2605
Gly Val Ile Ala Asp Pro Ser Ser Lys Thr Leu Ser Phe Phe Asn Lys
    2610                2615                2620
Asp Thr Arg Gly Glu Val Gln Thr Val Thr Phe Asp Thr Glu Glu Val
2625                2630                2635                2640
Lys Thr Leu Phe Tyr Gly Ser Phe His Lys Val His Ile Val Val Thr
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2645 2650 2655
Ser Lys Ser Val Lys Ile Tyr Ile Asp Cys Tyr Glu Ile Ile Glu Lys
2660 2665 2670
Asp Ile Lys Glu Ala Gly Asn Ile Thr Thr Asp Gly Tyr Glu Ile Leu
2675 2680 2685
Gly Lys Leu Leu Lys Gly Glu Arg Lys Ser Ala Ala Phe Gln Ile Gln
2690 2695 2700
Ser Phe Asp Ile Val Cys Ser Pro Val Trp Thr Ser Arg Asp Arg Cys
2705 2710 2715 2720
Cys Asp Ile Pro Ser Arg Arg Asp Glu Gly Lys Cys Pro Ala Phe Pro
2725 2730 2735
Asn Ser Cys Thr Cys Thr Gln Asp Ser Val Gly Pro Pro Gly Pro Pro
2740 2745 2750
Gly Pro Ala Gly Gly Pro Gly Ala Lys Gly Pro Arg Gly Glu Arg Gly
2755 2760 2765
Ile Ser Gly Ala Ile Gly Pro Pro Gly Pro Arg Gly Asp Ile Gly Pro
2770 2775 2780
Pro Gly Pro Gln Gly Pro Pro Gly Pro Gln Gly Pro Asn Gly Leu Ser
2785 2790 2795 2800
Ile Pro Gly Glu Gln Gly Arg Gln Gly Met Lys Gly Asp Ala Gly Glu
2805 2810 2815
Pro Gly Leu Pro Gly Arg Thr Gly Thr Pro Gly Leu Pro Gly Pro Pro
2820 2825 2830
Gly Pro Met Gly Pro Pro Gly Asp Arg Gly Phe Thr Gly Lys Asp Ser
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Ala Met Gly Pro Arg Gly Pro Pro Gly Arg Pro Gly Ser Pro Gly Ser
2850 2855 2860
Pro Gly Val Thr Gly Pro Ser Gly Lys Pro Gly Lys Pro Gly Asp His
2865 2870 2875 2880
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2885 2890 2895
Asp Ile Ala Ser Gln Asn Met Met Arg Ala Val Ala Arg Gln Val Cys
2900 2905 2910
Glu Gln Leu Ile Ser Gly Gln Met Asn Arg Phe Asn Gln Met Leu Asn
2915 2920 2925
Gln Ile Pro Asn Asp Tyr Gln Ser Ser Arg Asn Gln Pro Gly Pro Pro
2930 2935 2940
Gly Pro Pro Gly Pro Pro Gly Ser Ala Gly Ala Arg Gly Glu Pro Gly
2945 2950 2955 2960
Pro Gly Gly Arg Pro Gly Phe Pro Gly Thr Pro Gly Met Gln Gly Pro
2965 2970 2975
Pro Gly Glu Arg Gly Leu Pro Gly Glu Lys Gly Glu Arg Gly Thr Gly
2980 2985 2990
Ser Ser Gly Pro Arg Gly Leu Pro Gly Pro Pro Gly Pro Gln Gly Glu
2995 3000 3005
Ser Arg Thr Gly Pro Pro Gly Ser Thr Gly Ser Arg Gly Pro Pro Gly
3010 3015 3020
Pro Pro Gly Arg Pro Gly Asn Ser Gly Ile Gln Gly Pro Pro Gly Pro
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Gln Ser Tyr Pro Gly Ser Gly
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180

tcatcaccaa actgtgcacc agaatgtaac tgccctgaaa gctacccaag tgccatgtac
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1620
tagaattatt tttcactcta agtcatgtat gtttctcttt gattatttgc atgttatgtt
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<212> PRT
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35 40 45
Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val

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    50                  55                  60
Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
65                  70                  75                  80
Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
                85                  90                  95
Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
            100                 105                 110
Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
        115                 120                 125
Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
    130                 135                 140
Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
145                 150                 155                 160
Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
                165                 170                 175
Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
            180                 185                 190
Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
        195                 200                 205
Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
    210                 215                 220
Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
225                 230                 235                 240
Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu
                245                 250                 255
Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
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Ser Lys Leu Arg Leu Thr Ser Pro Pro Glu Pro Thr Val Met Thr His
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Val Pro Tyr Gln Val Leu Ala Leu Tyr Asn Ser Thr Arg Glu Leu Leu
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Glu Glu Met His Gly Glu Arg Glu Glu Gly Cys Thr Gln Glu Asn Thr
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Glu Ser Glu Tyr Tyr Ala Lys Glu Ile His Lys Phe Asp Met Ile Gln
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Gly Leu Ala Glu His Asn Glu Leu Ala Val Cys Pro Lys Gly Ile Thr
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Ser Lys Arg Asn Glu Gln Arg Ile Glu Leu Phe Gln Ile Leu Arg Pro
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Asp Glu His Ile Ala Lys Gln Arg Tyr Ile Gly Gly Lys Asn Leu Pro
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Thr Arg Gly Thr Ala Glu Trp Leu Ser Phe Asp Val Thr Asp Thr Val
195 200 205
Arg Glu Trp Leu Leu Arg Arg Glu Ser Asn Leu Gly Leu Glu Ile Ser
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Asn Ile His Glu Val Met Glu Ile Lys Phe Lys Gly Val Asp Asn Glu

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Tyr Ile Asp Phe Arg Gln Asp Leu Gly Trp Lys Trp Val His Glu Pro
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Lys Gly Tyr Tyr Ala Asn Phe Cys Ser Gly Pro Cys Pro Tyr Leu Arg
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Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro
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65 70 75 80
Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met
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Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro
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130 135 140
Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly
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Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe
165 170 175
Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro
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Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly
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Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg
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225 230 235 240
Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly
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Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn
260 265 270
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Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly
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Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala
305 310 315 320
Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala
325 330 335
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Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro
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Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn
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Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His
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Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
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Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly
625 630 635 640
Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu
645 650 655
Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp
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675 680 685
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gtcgcctacg ctttcgacac gcacacgggc accgacgcac gcccccagct gccgttcctc
1920
aacgagcacg cctacaccac ccagatcgac tacaacccca aggagcgggt gctgtacgcc
1980
tgggacaatg gccaccagct cacctacacc ctccacttcg tggtctga
2028

<210> 267

<211> 675
<212> PRT
<213> Homo sapiens

<400> 267
Met Ala Tyr Ala Lys Ala Leu Arg Leu Gln Trp Arg Glu Pro Leu Lys
1 5 10 15
Gly Lys Gly Asn Lys Glu Arg Phe Lys Gly Glu Tyr Gln Leu Thr Trp
20 25 30
Ala Leu Lys Ala Thr His Cys Leu Ala Ala Thr His Trp Ser Pro Ser
35 40 45
Cys Pro Pro Gln Gln Val Phe Gly Asp Leu Asp Gln Val Arg Met Thr
50 55 60
Ser Glu Gly Ser Asp Cys Arg Cys Lys Cys Ile Met Arg Pro Leu Ser
65 70 75 80
Lys Asp Ala Cys Ser Arg Val Arg Ser Gly Arg Ala Arg Val Glu Asp
85 90 95
Phe Tyr Thr Val Glu Thr Val Ser Ser Gly Thr Asp Cys Arg Cys Ser
100 105 110
Cys Thr Ala Pro Pro Ser Ser Leu Asn Pro Cys Glu Asn Glu Trp Lys
115 120 125
Met Glu Lys Leu Lys Lys Gln Ala Pro Glu Leu Leu Lys Leu Gln Ser
130 135 140
Met Val Asp Leu Leu Glu Gly Thr Leu Tyr Ser Met Asp Leu Met Lys
145 150 155 160
Val His Ala Tyr Val His Lys Val Ala Ser Gln Met Asn Thr Leu Glu
165 170 175
Glu Ser Ile Lys Ala Asn Leu Ser Arg Glu Asn Glu Val Val Lys Asp
180 185 190
Ser Val Arg His Leu Ser Glu Gln Leu Arg His Tyr Glu Asn His Ser
195 200 205
Ala Ile Met Leu Gly Ile Lys Lys Glu Leu Ser Arg Leu Gly Leu Gln
210 215 220
Leu Leu Gln Lys Asp Ala Ala Ala Ala Pro Ala Thr Pro Ala Thr Gly
225 230 235 240
Thr Gly Ser Lys Ala Gln Asp Thr Ala Arg Gly Lys Gly Lys Asp Ile
245 250 255
Ser Lys Tyr Gly Ser Val Gln Lys Ser Phe Ala Asp Arg Gly Leu Pro
260 265 270
Lys Pro Pro Lys Glu Lys Leu Leu Gln Val Glu Lys Leu Arg Lys Glu
275 280 285
Ser Gly Lys Gly Ser Phe Leu Gln Pro Thr Ala Lys Pro Arg Ala Leu
290 295 300
Ala Gln Gln Gln Ala Val Ile Arg Gly Phe Thr Tyr Tyr Lys Ala Gly
305 310 315 320
Lys Gln Glu Val Thr Glu Ala Val Ala Asp Asn Thr Leu Gln Gly Thr
325 330 335
Ser Trp Leu Glu Gln Leu Pro Pro Lys Val Glu Gly Arg Ser Asn Ser
340 345 350
Ala Glu Pro Asn Ser Ala Glu Gln Asp Glu Ala Glu Pro Arg Ser Ser
355 360 365
Glu Arg Val Asp Leu Ala Ser Gly Thr Pro Thr Ser Ile Pro Ala Thr
370 375 380
Thr Thr Thr Ala Thr Thr Thr Pro Thr Pro Thr Thr Ser Leu Leu Pro
385 390 395 400
Thr Glu Pro Pro Ser Gly Pro Glu Val Ser Ser Gln Gly Arg Glu Ala
405 410 415
Ser Cys Glu Gly Thr Leu Arg Ala Val Asp Pro Pro Val Arg His His
420 425 430
Ser Tyr Gly Arg His Glu Gly Ala Trp Met Lys Asp Pro Ala Ala Arg
435 440 445
Asp Asp Arg Ile Tyr Val Thr Asn Tyr Tyr Tyr Gly Asn Ser Leu Val
450 455 460
Glu Phe Arg Asn Leu Glu Asn Phe Lys Gln Gly Arg Trp Ser Asn Met
465 470 475 480
Tyr Lys Leu Pro Tyr Asn Trp Ile Gly Thr Gly His Val Val Tyr Gln

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                    485                     490                     495
Gly Ala Phe Tyr Tyr Asn Arg Ala Phe Thr Lys Asn Ile Ile Lys Tyr
                500                     505                     510
Asp Leu Arg Gln Arg Phe Val Ala Ser Trp Ala Leu Leu Pro Asp Val
            515                     520                     525
Val Tyr Glu Asp Thr Thr Pro Trp Lys Trp Arg Gly His Ser Asp Ile
    530                     535                     540
Asp Phe Ala Val Asp Glu Ser Gly Leu Trp Val Ile Tyr Pro Ala Val
545                     550                     555                     560
Asp Asp Arg Asp Glu Ala Gln Pro Glu Val Ile Val Leu Ser Arg Leu
                565                     570                     575
Asp Pro Gly Asp Leu Ser Val His Arg Glu Thr Thr Trp Lys Thr Arg
                580                     585                     590
Leu Arg Arg Asn Ser Tyr Gly Asn Cys Phe Leu Val Cys Gly Ile Leu
            595                     600                     605
Tyr Ala Val Asp Thr Tyr Asn Gln Gln Glu Gly Gln Val Ala Tyr Ala
    610                     615                     620
Phe Asp Thr His Thr Gly Thr Asp Ala Arg Pro Gln Leu Pro Phe Leu
625                     630                     635                     640
Asn Glu His Ala Tyr Thr Thr Gln Ile Asp Tyr Asn Pro Lys Glu Arg
                645                     650                     655
Val Leu Tyr Ala Trp Asp Asn Gly His Gln Leu Thr Tyr Thr Leu His
                660                     665                     670
Phe Val Val
        675
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<210> 268
<211> 1909
<212> DNA
<213> Homo sapiens

<400> 268
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gacacctttt aaaatgcaga actaactgag gcatttcagt aactttgctt tcaaatcaat
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aaagtcaaat gtatggaaac attttgtgcc ctactctcca taccctgtgt actcaaattc
120
tctactgtat gaattatgct ttaagtagaa ttcagtgcca aggagaactt ggtgaaataa
180
attattttaa tttttttttt atcctttaca aagccatgga ttttatttgg ttgatgtgtg
240
ctctgtacac aagccatttc aataggatgg agctgttaat tattttccaa agagtaatag
300
acatgcaaaa gtttcaataa aaactgggcc attaacaaat aaattaataa actaataagc
360
attcccttct aggtttttgc caaactgcct atccaataac aaatttgaga atcgttgaaa
420
aagctagtta tatttcagag aaatgatttt cattattgaa actgttctcc ctagcaggcc
480
attttccctt tttcctggga gtttagcaag tttaggagag aatagtcatg aaaagaaagg
540
gaagaaaggg gagaagggaa gaggttaaaa agtaagtgct cagacctatg aacgtaatcc
600
ctttgctaga aatatttaag agcagctcag cttggttgaa actgagtttt gtcatcttcc
660
atatttgcag gaaggtattt tctgacttgc aatgcagcta gatgtaaaat tttattttat
720
catcctagaa agccttgact agaaaaatga ataaatattg agggtttcct gtccatatct
780
ggcttgcatg tgccagaaag cagagaatag aaaatgtaat ctccaacatc caagcatcga
840
aacccaaggg gtaggcaatt ctatgtaggt tttggacatg aagtttggtg catcttggtt
900
tatgctggct caactgctat taaacctctc tggcttatag tctcttcatt ctattagaca
960
agcacgtatc gaacacttgc ttcgcacaag gctctttagt taacaattta gcagctactg
1020
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tttgtgttaa acacactttt caccaaatag gttctgaggc aaacgagagc aatgactatt
1080
taaagaaagg ctttcccagc atcacttaca catcccaaaa ctaaaaagat caactcttcc
1140
aactgagaaa agactcctgg ctttgaatgg aaacttacag cagagagtca caggccacgg
1200
caacaacaac gacaacaaca aacatttgga atattattct caactcacgt tttaataata
1260
catcttaatt atttttctag tagagaaact acaaatcagc ctcttcaaca tttatataca
1320
gtttaataag cctcttgcaa gttacttgtt ctctcacctg aggtattttt ttcctcccca
1380
ccttgcccct gttcctccct tcctcttctc cctttgcaag aggaaatatt taacatattt
1440
gggtccaact tcaataatgt aataattaat acattaaaag catttaactt cctttctaga
1500
aaaatgcaca ggctaaggca tagacaaaac aaagagaaat gctgagaaat ttgccactgg
1560
agacaagcaa tctgaataaa tatttgccaa aagttctttt tatgtcatat agtgtcagga
1620
tttgaaggag ctattttttt taatgttgca actagcaact catcttcgga agacacagcc
1680
aggagaatga agtagaagtg aaaggtttat aaatccattt gtaagcattt atcccatata
1740
ttttaaattc aagaaaaatt gtgtttatct ttagaatttt gtattcaata ctttatgtac
1800
tatgtgactc atgcttctgg ataaataaag caccaaatat gtatctgtaa ccacaatcac
1860
acatattata ttaaatatat atctatataa caaaaaaaaa aaaaaaaaa
1909

<210> 269
<211> 83
<212> PRT
<213> Homo sapiens

<400> 269
Met Tyr Gly Asn Ile Leu Cys Pro Thr Leu His Thr Leu Cys Thr Gln
1 5 10 15
Ile Leu Tyr Cys Met Asn Tyr Ala Leu Ser Arg Ile Gln Cys Gln Gly
20 25 30
Glu Leu Gly Glu Ile Asn Tyr Phe Asn Phe Phe Phe Ile Leu Tyr Lys
35 40 45
Ala Met Asp Phe Ile Trp Leu Met Cys Ala Leu Tyr Thr Ser His Phe
50 55 60
Asn Arg Met Glu Leu Leu Ile Ile Phe Gln Arg Val Ile Asp Met Gln
65 70 75 80
Lys Phe Gln

<210> 270
<211> 1720
<212> DNA
<213> Homo sapiens

<400> 270
gactgcagat gaaattagta actggtgggg tcgtggggtg tgaatggtgg gcgggagcag
60
ctatgtcagt tggtgtgttt ctgcttatgt tagggtaatt gggcacggcc tttgtgtaac
120
tggtgaatat ctctgaacct gggcatgaaa cagagagatg tcctaactct gggtgagagg
180
aatcctcatt tttctctgcc ctctcactgt ggcatcctaa gaaaaaagtt ttgggttcct
240
gcagcatgaa ggagagctct gctcccagaa tttgggagct ccagatttct tccagggtgt
300

ggaggcatca atatatcagt ctgggaaagg ggttcctggg ccactccagg agctgagttg
360
ggtggaaggt gctgagagtg tgggtggggg ccacttctga gcacccatgt ggcacccact
420
gctggtccct gtttgtggct gggcactcag gaaaatgttt ttggtgctaa gagtaaaaag
480
ccaaccaaca aacacatctc ttttttctgt ctattcactg gaaagtaaaa gcagtctggg
540
cgcaggctgg ggacccagat ggaattcaaa cttatgcctg ctctcaaggt gctcacggtt
600
gctgataaac agctggataa aatgaagagt ctatgagtga gggatgcaga gccagggaag
660
gctggtggag tgatgccacc agcacagggg tatgagtttg cagctgccaa ggggccaagg
720
gatgagctgg ggccctcctt cccaatggca tctccccctg gtctggaact gaagacactg
780
agcaatggtc cccaagcccc aaggagatca gctcccctgg gcccagtggc cccaaccagg
840
gagggtgtgg agaatgcctg cttctcctca gaggagcatg agacccattt ccagaacccct
900
gggaacacga gactgggcag ctcacccagt ccccctgggg gtgtctcctc actgccccga
960
tcccagcggg atgatctgtc ccttcattca gaggaggggc cagccctgga gcccgtgagc
1020
cgcccggtgg attatggctt tgtttccgcc ctcgttttcc tggtgagtgg gattcttctg
1080
gtggtgacag catacgccat cccccgtgag gctcgagtca atccggacac agtgacagcg
1140
cgggagatgg aacgactgga gatgtactac gcccgcctag gctcccacct ggacaggtgc
1200
atcatcgcag gcctcgggct gctcacggtg ggcggcatgc tcttgtcggt gctgctcatg
1260
gtctccctgt gcaagggcga gctgtaccgc cggaggacct tcgtccccgg caagggctcc
1320
aggaagacct acggctccat taacctgcgc atgagacagc tcaatgggga tgggggccag
1380
gccctggtgg agaatgaagt tgtccaggtc tcagagacta gccacaccct ccagaggtct
1440
taagaactag cccaccttat ctggctgctt tagctccagt gctacaaggt ccaccccctg
1500
ctcccgccca cctgacccct gccaaggccc tggggtttta aactgagctc acatagggcc
1560
ttgtggaaga agtactgggt gctggaggga gagctcgggg cccagcccat gccccacacg
1620
ggcaagcagc ccactgatct gttttgtagc tgaggttttg catacggttt tgtttggagg
1680
atggcttctg ctgctaaaaa tacaaaagtt tggaaaccgc
1720

<210> 271
<211> 256
<212> PRT
<213> Homo sapiens

<400> 271
Met Pro Pro Ala Gln Gly Tyr Glu Phe Ala Ala Ala Lys Gly Pro Arg
1 5 10 15
Asp Glu Leu Gly Pro Ser Phe Pro Met Ala Ser Pro Pro Gly Leu Glu
20 25 30
Leu Lys Thr Leu Ser Asn Gly Pro Gln Ala Pro Arg Arg Ser Ala Pro
35 40 45
Leu Gly Pro Val Ala Pro Thr Arg Glu Gly Val Glu Asn Ala Cys Phe
50 55 60
Ser Ser Glu Glu His Glu Thr His Phe Gln Asn Pro Gly Asn Thr Arg
65 70 75 80
Leu Gly Ser Ser Pro Ser Pro Pro Gly Gly Val Ser Ser Leu Pro Arg

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                85                      90                      95
Ser Gln Arg Asp Asp Leu Ser Leu His Ser Glu Glu Gly Pro Ala Leu
            100                     105                     110
Glu Pro Val Ser Arg Pro Val Asp Tyr Gly Phe Val Ser Ala Leu Val
        115                     120                     125
Phe Leu Val Ser Gly Ile Leu Leu Val Val Thr Ala Tyr Ala Ile Pro
    130                     135                     140
Arg Glu Ala Arg Val Asn Pro Asp Thr Val Thr Ala Arg Glu Met Glu
145                     150                     155                     160
Arg Leu Glu Met Tyr Tyr Ala Arg Leu Gly Ser His Leu Asp Arg Cys
                165                     170                     175
Ile Ile Ala Gly Leu Gly Leu Leu Thr Val Gly Gly Met Leu Leu Ser
            180                     185                     190
Val Leu Leu Met Val Ser Leu Cys Lys Gly Glu Leu Tyr Arg Arg Arg
        195                     200                     205
Thr Phe Val Pro Gly Lys Gly Ser Arg Lys Thr Tyr Gly Ser Ile Asn
    210                     215                     220
Leu Arg Met Arg Gln Leu Asn Gly Asp Gly Gly Gln Ala Leu Val Glu
225                     230                     235                     240
Asn Glu Val Val Gln Val Ser Glu Thr Ser His Thr Leu Gln Arg Ser
                245                     250                     255
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<210> 272
<211> 1111
<212> DNA
<213> Homo sapiens

<400> 272
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acgccatcaa gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag
120
ctgagcaggc ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg
180
agctggtgtc actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaatactctg
240
aggctctcaa agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg
300
aagccgacgt agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcgtg
360
cccaggagcg tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg
420
agagtgagag aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg
480
aaattcagga gatccaactg aaagaggcca agcacattgc tgaagatgcc gaccgcaaat
540
acgaagaggt ggcccgtaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc
600
gggctgagct ctcagaaggc aaatgtgccg agcttgaaga agaattgaaa actgtgacga
660
acaacttgaa gtcactggag gctcaggctg agaagtactc gcagaaggaa gacagatatg
720
aggaagagat caaggtcctt tccgacaagc tgaaggaggc tgagactcgg gctgagtttg
780
cggagaggtc agtaactaaa ttggagaaaa gcattgatga cttagaagac gagctgtacg
840
ctcagaaact gaagtacaaa gccatcagcg aggagctgga ccacgctctc aacgatatga
900
cttccatata agtttctttg cttcacttct cccaagactc cctcgtcgag ctggatgtcc
960
cacctctctg agctctgcat ttgtctattc tccagctgac cctggttctc tctcttagca
1020
tcctgcctta gagccaggca cacactgtgc tttctattgt acagaagctc ttcgtttcag
1080
tgtcaaataa acactgtgta agctaaaaaa a
1111

<210> 273
<211> 284
<212> PRT
<213> Homo sapiens

<400> 273
Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
1   5   10   15
Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
            20   25   30
Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
        35   40   45
Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
    50   55   60
Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
65   70   75   80
Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
                85   90   95
Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
            100   105   110
Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
        115   120   125
Val Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln
    130   135   140
Glu Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg
145   150   155   160
Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu
                165   170   175
Glu Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu
            180   185   190
Leu Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu
        195   200   205
Ala Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu
    210   215   220
Ile Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225   230   235   240
Phe Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu
                245   250   255
Glu Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu
            260   265   270
Glu Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile
        275   280

<210> 274
<211> 2032
<212> DNA
<213> Homo sapiens

<400> 274
caccccgcag cccggcctcg gcctccgccg cttgttgtcg cgcccccgccc gcgagcccgc
60
cccgcacgtc ccccgccggc ggccaccatg agcacaggcc tgcggtacaa gagcaagctg
120
gcgaccccag aggacaagca ggacattgac aagcagtacg tgggcttcgc cacactgccc
180
aaccaggtgc accgcaagtc ggtgaagaaa ggctttgact tcacactcat ggtggctggt
240
gagtcaggcc tggggaagtc cacactggtc cacagcctct tcctgacaga cttgtacaag
300
gaccggaagc tgctcagtgc tgaggagcgc atcagccaga cggtagagat tctaaaacac
360
acggtggaca ttgaggagaa gggagtcaag ctgaagctca ccatcgtgga cacgccggga
420
ttcggggacg ctgtcaacaa caccgagtgc tggaagccca tcaccgacta tgtggaccag
480

cagtttgagc agtacttccg tgatgagagc ggcctcaacc gaaagaacat ccaagacaac
540
cgagtgcact gctgcctata cttcatctcc cccttcgggc atgggctgcg gccagtggat
600
gtgggtttca tgaaggcatt gcatgagaag gtcaacatcg tgcctctcat cgccaaagct
660
gactgtcttg tccccagtga gatccggaag ctgaaggagc ggatccggga ggagattgac
720
aagtttggga tccatgtata ccagttccct gagtgtgact cggacgagga tgaggacttc
780
aagcagcagg accgggaact gaaggagagc gcgccccttcg ccgttatagg cagcaacacg
840
gtggtggagg ccaaggggca gcgggtccgg ggccgactgt accccctgggg gatcgtggag
900
gtggagaacc aggcgcattg cgacttcgtg aagctgcgca acatgctcat ccgcacgcat
960
atgcacgacc tcaaggacgt gacgtgcgac gtgcactacg agaactaccg cgcgcactgc
1020
atccagcaga tgaccagcaa actgacccag gacagccgca tggagagccc catcccgatc
1080
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1200
tcgccgcgga cacaccgtcc gtctccggga cgccctcgca cccctggaca ccagaccgga
1260
ctgttcccga cccggagacg cggggccaca gcccccagct gaccctaatt tattctcagc
1320
accacccccct cccaggtcat tgtgtctgtt tccgaggggc ctggaccgta gcccccgccc
1380
agctggccct ctctgacctt gggggatcag gagcgaagtt gggcgggact tcagagatcc
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1500
ctggcaggca ggcaaagcta ggcagaagag gattcccagg atcctgggtc tgttccctgc
1560
cccagtgctg cagaacggac ttgggagccc tcctttgcct gctcccgcgg gtcacccagc
1620
gagtgctgag accccatttt ctgtcgaggc gggccgagtc ttcccttatc cccagacgcc
1680
tagcgggcag ggttgggctg aatcaaatgg gagccctcca gacataagga ggccagaggc
1740
tgcaaggagc ggggtcgtga ccgcttacac cccttctcca cagcccggcc cgacctggag
1800
ggcccccggg gcactgggcg gtgagccacc tcctggcaac tctcggtgcc gtcccctgcc
1860
ctcgctcgag gcctcttctc cccagcaccg ctgtggtgtg ccgggatcct gagcctaggc
1920
ctcccgatgt tcccacccgc atgatccctt cccgccacac gatgctccgt tttcttccgt
1980
tgtgaatgcc gcgtcctgtc ctggtgacag gagaacaatg ttggtgaacg tc
2032

<210> 275
<211> 369
<212> PRT
<213> Homo sapiens

<400> 275
Met Ser Thr Gly Leu Arg Tyr Lys Ser Lys Leu Ala Thr Pro Glu Asp
1 5 10 15
Lys Gln Asp Ile Asp Lys Gln Tyr Val Gly Phe Ala Thr Leu Pro Asn
20 25 30
Gln Val His Arg Lys Ser Val Lys Lys Gly Phe Asp Phe Thr Leu Met
35 40 45
Val Ala Gly Glu Ser Gly Leu Gly Lys Ser Thr Leu Val His Ser Leu

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    50                  55                  60
Phe Leu Thr Asp Leu Tyr Lys Asp Arg Lys Leu Leu Ser Ala Glu Glu
65                  70                  75                  80
Arg Ile Ser Gln Thr Val Glu Ile Leu Lys His Thr Val Asp Ile Glu
                85                  90                  95
Glu Lys Gly Val Lys Leu Lys Leu Thr Ile Val Asp Thr Pro Gly Phe
            100                 105                 110
Gly Asp Ala Val Asn Asn Thr Glu Cys Trp Lys Pro Ile Thr Asp Tyr
        115                 120                 125
Val Asp Gln Gln Phe Glu Gln Tyr Phe Arg Asp Glu Ser Gly Leu Asn
    130                 135                 140
Arg Lys Asn Ile Gln Asp Asn Arg Val His Cys Cys Leu Tyr Phe Ile
145                 150                 155                 160
Ser Pro Phe Gly His Gly Leu Arg Pro Val Asp Val Gly Phe Met Lys
                165                 170                 175
Ala Leu His Glu Lys Val Asn Ile Val Pro Leu Ile Ala Lys Ala Asp
            180                 185                 190
Cys Leu Val Pro Ser Glu Ile Arg Lys Leu Lys Glu Arg Ile Arg Glu
        195                 200                 205
Glu Ile Asp Lys Phe Gly Ile His Val Tyr Gln Phe Pro Glu Cys Asp
    210                 215                 220
Ser Asp Glu Asp Glu Asp Phe Lys Gln Gln Asp Arg Glu Leu Lys Glu
225                 230                 235                 240
Ser Ala Pro Phe Ala Val Ile Gly Ser Asn Thr Val Val Glu Ala Lys
                245                 250                 255
Gly Gln Arg Val Arg Gly Arg Leu Tyr Pro Trp Gly Ile Val Glu Val
            260                 265                 270
Glu Asn Gln Ala His Cys Asp Phe Val Lys Leu Arg Asn Met Leu Ile
        275                 280                 285
Arg Thr His Met His Asp Leu Lys Asp Val Thr Cys Asp Val His Tyr
    290                 295                 300
Glu Asn Tyr Arg Ala His Cys Ile Gln Gln Met Thr Ser Lys Leu Thr
305                 310                 315                 320
Gln Asp Ser Arg Met Glu Ser Pro Ile Pro Ile Leu Pro Leu Pro Thr
                325                 330                 335
Pro Asp Ala Glu Thr Glu Lys Leu Ile Arg Met Lys Asp Glu Glu Leu
            340                 345                 350
Arg Arg Met Gln Glu Met Leu Gln Arg Met Lys Gln Gln Met Gln Asp
        355                 360                 365
Gln
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<210> 276
<211> 1344
<212> DNA
<213> Homo sapiens

<400> 276

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ctggaaaggg aaaaaaggca gcattcacca catcccaatc ctgaatccaa gagtctaaga
120
tagtccccca ctcctatctc aggcttagag gattagatta atctcctgga gggaagactc
180
ttccttgaaa cattttttt tatctgcctg tagctattgg gataattcgg gaaatccaca
240
gggacagttc aagtcatctt tgtcctctac tttctgttgc actctcagcc ttgttctctt
300
tttagaaact gcatggtaac tattatatag ctaaagaaga gcattctgac ctctgccctg
360
ggacttcctg gatcctcctc ttcttataaa tacaagggca gagctggtat cccggggagc
420
caggaagcag tgagcccagg agtcctcggc cagccctgcc tgcccaccag gaggatgaag
480
gtctccgtgg ctgccctctc ctgcctcatg cttgttgctg tccttggatc ccaggcccag
540
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ttcacaaatg atgcagagac agagttaatg atgtcaaagc ttccactgga aatccagta
600
gttctgaaca gctttcactt tgctgctgac tgctgcacct cctacatctc acaaagcatc
660
ccgtgttcac tcatgaaaag ttattttgaa acgagcagcg agtgctccaa gccaggtgtc
720
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960
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1020
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1200
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1344

<210> 277
<211> 93
<212> PRT
<213> Homo sapiens

<400> 277
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1 5 10 15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 278
<211> 1344
<212> DNA
<213> Homo sapiens

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360

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720
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780
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1200
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1344

<210> 279
<211> 93
<212> PRT
<213> Homo sapiens

<400> 279
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
1 5 10 15
Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 280
<211> 1344
<212> DNA
<213> Homo sapiens

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180

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240
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300
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360
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420
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600
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720
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780
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960
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1020
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1200
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1344

<210> 281
<211> 93
<212> PRT
<213> Homo sapiens

<400> 281
Met Lys Ile Ser Val Ala Ala Ile Pro Phe Phe Leu Leu Ile Thr Ile
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Ala Leu Gly Thr Lys Thr Glu Ser Ser Ser Arg Gly Pro Tyr His Pro
20 25 30
Ser Glu Cys Cys Phe Thr Tyr Thr Thr Tyr Lys Ile Pro Arg Gln Arg
35 40 45
Ile Met Asp Tyr Tyr Glu Thr Asn Ser Gln Cys Ser Lys Pro Gly Ile
50 55 60
Val Phe Ile Thr Lys Arg Gly His Ser Val Cys Thr Asn Pro Ser Asp
65 70 75 80
Lys Trp Val Gln Asp Tyr Ile Lys Asp Met Lys Glu Asn
85 90

<210> 282
<211> 2750
<212> DNA
<213> Homo sapiens

<400> 282

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180
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240
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300
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360
ttaccaacat ccagtgggat ccccgtggat tctccctacc ccttttaag aggattgttg
420
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540
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1980

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2750

<210> 283
<211> 380
<212> PRT
<213> Homo sapiens

<220>
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<223> Xaa = Any Amino Acid

<400> 283
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Asp Lys Thr Ile Arg Ser Thr Thr Asp Pro Val Met Ser Gln Cys Ala
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Cys Leu Glu Glu Val His Leu Pro Asn Ile Lys Pro Gly Glu Gly Leu
35 40 45
Gly Met Tyr Ile Lys Ser Thr Tyr Asp Gly Leu His Val Ile Thr Gly
50 55 60
Thr Thr Glu Asn Ser Pro Ala Asp Arg Ser Gln Lys Ile His Ala Gly
65 70 75 80
Asp Glu Val Ile Gln Val Asn Gln Gln Thr Val Val Gly Trp Gln Leu
85 90 95
Lys Asn Leu Val Lys Lys Leu Arg Glu Asn Pro Thr Gly Val Val Leu
100 105 110
Leu Leu Lys Lys Arg Pro Thr Gly Ser Phe Asn Phe Thr Pro Ala Pro
115 120 125
Leu Lys Asn Leu Arg Trp Lys Pro Pro Leu Val Gln Thr Ser Pro Pro
130 135 140
Pro Ala Thr Thr Gln Ser Pro Glu Ser Thr Met Asp Thr Ser Leu Lys
145 150 155 160
Lys Glu Lys Ser Ala Ile Leu Asp Leu Tyr Ile Pro Pro Pro Pro Ala
165 170 175
Val Pro Tyr Ser Pro Arg Asp Glu Asn Gly Ser Phe Val Tyr Gly Gly
180 185 190
Ser Ser Lys Cys Lys Gln Pro Leu Pro Gly Pro Lys Gly Ser Glu Ser
195 200 205
Pro Asn Ser Phe Leu Asp Gln Glu Ser Arg Arg Arg Arg Phe Thr Ile
210 215 220

Ala Asp Ser Asp Gln Leu Pro Gly Tyr Ser Val Glu Thr Asn Ile Leu
225 230 235 240
Pro Thr Lys Met Arg Glu Lys Thr Pro Ser Tyr Xaa Lys Pro Arg Pro
245 250 255
Leu Ser Met Pro Ala Asp Gly Asn Trp Met Gly Ile Val Asp Pro Phe
260 265 270
Ala Arg Pro Arg Gly His Gly Arg Lys Gly Glu Asp Ala Leu Cys Arg
275 280 285
Tyr Phe Ser Asn Glu Arg Ile Pro Pro Ile Ile Glu Glu Ser Ser Ser
290 295 300
Pro Pro Tyr Arg Phe Ser Arg Pro Thr Thr Glu Arg His Leu Val Arg
305 310 315 320
Gly Ala Asp Tyr Ile Arg Gly Ser Arg Cys Tyr Ile Asn Ser Asp Leu
325 330 335
His Ser Ser Ala Thr Ile Pro Phe Gln Glu Glu Gly Thr Lys Lys Lys
340 345 350
Ser Gly Ser Ser Ala Thr Lys Ser Ser Ser Thr Glu Pro Ser Leu Leu
355 360 365
Val Ser Trp Phe Thr Arg Leu Lys Leu Leu Thr His
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<210> 284
<211> 1789
<212> DNA
<213> Homo sapiens

<400> 284
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1680
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1789

<210> 285
<211> 335
<212> PRT
<213> Homo sapiens

<400> 285
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Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
20 25 30
Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
50 55 60
Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65 70 75 80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
85 90 95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
100 105 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
115 120 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
130 135 140
Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145 150 155 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
165 170 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
180 185 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
195 200 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
210 215 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
225 230 235 240
Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
245 250 255
Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
260 265 270
Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
275 280 285
Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro Cys Thr

290 295 300
Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val Gln Glu
305 310 315 320
Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu Ser
325 330 335

<210> 286
<211> 305
<212> PRT
<213> Homo sapiens

<400> 286
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20 25 30
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35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val
50 55 60
Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65 70 75 80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
85 90 95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
100 105 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
115 120 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
130 135 140
Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145 150 155 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
165 170 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
180 185 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
195 200 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
210 215 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Gly Lys Thr Asn His Tyr Gln
225 230 235 240
Thr Thr Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys
245 250 255
Pro Gly Pro Leu Gln Lys Lys Leu Asp Ser Phe Pro Ala Gln Asp Pro
260 265 270
Cys Thr Thr Ile Tyr Val Ala Ala Thr Glu Pro Val Pro Glu Ser Val
275 280 285
Gln Glu Thr Asn Ser Ile Thr Val Tyr Ala Ser Val Thr Leu Pro Glu
290 295 300
Ser
305

<210> 287
<211> 298
<212> PRT
<213> Homo sapiens

<400> 287
Met Asp Pro Lys Gly Leu Leu Ser Leu Thr Phe Val Leu Phe Leu Ser
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Leu Ala Phe Gly Ala Ser Tyr Gly Thr Gly Gly Arg Met Met Asn Cys
20 25 30
Pro Lys Ile Leu Arg Gln Leu Gly Ser Lys Val Leu Leu Pro Leu Thr
35 40 45
Tyr Glu Arg Ile Asn Lys Ser Met Asn Lys Ser Ile His Ile Val Val

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Thr Met Ala Lys Ser Leu Glu Asn Ser Val Glu Asn Lys Ile Val Ser
65                  70                  75                  80
Leu Asp Pro Ser Glu Ala Gly Pro Pro Arg Tyr Leu Gly Asp Arg Tyr
                85                  90                  95
Lys Phe Tyr Leu Glu Asn Leu Thr Leu Gly Ile Arg Glu Ser Arg Lys
            100                 105                 110
Glu Asp Glu Gly Trp Tyr Leu Met Thr Leu Glu Lys Asn Val Ser Val
        115                 120                 125
Gln Arg Phe Cys Leu Gln Leu Arg Leu Tyr Glu Gln Val Ser Thr Pro
    130                 135                 140
Glu Ile Lys Val Leu Asn Lys Thr Gln Glu Asn Gly Thr Cys Thr Leu
145                 150                 155                 160
Ile Leu Gly Cys Thr Val Glu Lys Gly Asp His Val Ala Tyr Ser Trp
                165                 170                 175
Ser Glu Lys Ala Gly Thr His Pro Leu Asn Pro Ala Asn Ser Ser His
            180                 185                 190
Leu Leu Ser Leu Thr Leu Gly Pro Gln His Ala Asp Asn Ile Tyr Ile
        195                 200                 205
Cys Thr Val Ser Asn Pro Ile Ser Asn Asn Ser Gln Thr Phe Ser Pro
    210                 215                 220
Trp Pro Gly Cys Arg Thr Asp Pro Ser Glu Thr Lys Pro Trp Ala Val
225                 230                 235                 240
Tyr Ala Gly Leu Leu Gly Gly Val Ile Met Ile Leu Ile Met Val Val
                245                 250                 255
Ile Leu Gln Leu Arg Arg Arg Gly Lys Thr Asn His Tyr Gln Thr Thr
            260                 265                 270
Val Glu Lys Lys Ser Leu Thr Ile Tyr Ala Gln Val Gln Lys Pro Gly
        275                 280                 285
Asp Thr His His Gln Thr Ser Asp Leu Phe
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<210> 288
<211> 3640
<212> DNA
<213> Homo sapiens

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Gly Gly Glu Val Ile Phe Lys Ala Leu Ser Pro Pro Tyr Asp Thr Glu
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Asn Arg Thr Arg Val Val Glu Asp Asn His Asn Tyr Tyr Val Ser Arg
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Ala Val Ala Asn Arg Ser His Val Lys Ile His Arg Ile Leu Ser Ser
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Tyr Gly His Pro Leu Arg Gln Ile Thr Ile Ala Thr Gly Gly Phe Ile
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Phe Met Gly Asp Met Leu His Arg Met Leu Thr Ala Thr Gln Tyr Val
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180 185 190
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Val Tyr Leu Gln Asp Arg Glu Asp Arg Gly Ser Phe Thr Phe Gln Ala
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Ala Leu His Arg Asp Gly Arg Ile Val Phe Gly Tyr Lys Glu Ile Pro
225 230 235 240
Met Ala Val Leu Asp Ile Ser Ser Ala Gln His Pro Val Lys Ala Gly
245 250 255
Leu Ser Asp Ala Phe Met Ile Leu Asn Ser Ser Pro Glu Val Pro Glu
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Ser Gln Arg Arg Thr Ile Phe Glu Tyr His Arg Val Glu Leu Asp Ser
275 280 285
Ser Lys Ile Thr Thr Thr Ser Ala Val Glu Phe Thr Pro Leu Pro Thr
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Cys Leu Gln His Gln Ser Cys Asp Thr Cys Val Ser Ser Asn Leu Thr
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Phe Asn Cys Ser Trp Cys His Val Leu Gln Arg Cys Ser Ser Gly Phe
325 330 335
Asp Arg Tyr Arg Gln Glu Trp Leu Thr Tyr Gly Cys Ala Gln Glu Ala
340 345 350
Glu Gly Lys Thr Cys Glu Asp Phe Gln Asp Asp Ser His Tyr Ser Ala
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Ser Pro Asp Ser Ser Phe Ser Pro Phe Asn Gly Asp Ser Thr Thr Ser
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Ser Ser Leu Phe Ile Asp Ser Leu Thr Thr Glu Asp Asp Thr Lys Leu

385 390 395 400
Asn Pro Tyr Ala Glu Gly Asp Gly Leu Pro Asp His Ser Ser Pro Lys
405 410 415
Ser Lys Gly Pro Pro Val His Leu Gly Thr Ile Val Gly Ile Val Leu
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Ala Val Leu Leu Val Ala Ala Ile Ile Leu Ala Gly Ile Tyr Ile Ser
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Gly His Pro Asn Ser Asn Ala Ala Leu Phe Phe Ile Glu Arg Arg Pro
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Trp Asn Glu Glu Gly Val Glu Val Asp Ser Gln Ala Tyr Asn His Arg
50 55 60
Trp Lys Arg Asn Val Asp Pro Phe Lys Ala Val Asp Thr Asn Arg Ala
65 70 75 80
Ser Met Gly Gln Ala Ser Pro Glu Ser Lys Gly Phe Thr Asp Leu Leu
85 90 95
Leu Asp Asp Gly Gln Asp Asn Asn Thr Gln Ile Glu Glu Asp Thr Asp
100 105 110
His Asn Tyr Tyr Ile Ser Arg Ile Tyr Gly Pro Ala Asp Ser Ala Ser
115 120 125
Arg Asp Leu Trp Val Asn Ile Asp Gln Met Glu Lys Asp Lys Val Lys
130 135 140
Ile His Gly Ile Leu Ser Asn Thr His Arg Gln Ala Ala Arg Val Asn
145 150 155 160
Leu Ser Phe Asp Phe Pro Phe Tyr Gly His Phe Leu Asn Glu Val Thr
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Val Ala Thr Gly Gly Phe Ile Tyr Thr Gly Glu Val Val His Arg Met
180 185 190
Leu Thr Ala Thr Gln Tyr Ile Ala Pro Leu Met Ala Asn Phe Asp Pro
195 200 205
Ser Val Ser Arg Asn Ser Thr Val Arg Tyr Phe Asp Asn Gly Thr Ala
210 215 220
Leu Val Val Gln Trp Asp His Val His Leu Gln Asp Asn Tyr Asn Leu
225 230 235 240
Gly Ser Phe Thr Phe Gln Ala Thr Leu Leu Met Asp Gly Arg Ile Ile
245 250 255
Phe Gly Tyr Lys Glu Ile Pro Val Leu Val Thr Gln Ile Ser Ser Thr
260 265 270
Asn His Pro Val Lys Val Gly Leu Ser Asp Ala Phe Val Val Val His

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325 330 335
Cys Val Ser Ser Gln Ile Gly Phe Asn Cys Ser Trp Cys Ser Lys Leu
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Gln Arg Cys Ser Ser Gly Phe Asp Arg His Arg Gln Asp Trp Val Asp
355 360 365
Ser Gly Cys Pro Glu Glu Val Gln Ser Lys Glu Lys Met Cys Glu Lys
370 375 380
Thr Glu Pro Gly Glu Thr Ser Gln Thr Thr Thr Thr Ser His Thr Thr
385 390 395 400
Thr Met Gln Phe Arg Val Leu Thr Thr Thr Arg Arg Ala Val Thr Ser
405 410 415
Gln Met Pro Thr Ser Leu Pro Thr Glu Asp Asp Thr Lys Ile Ala Leu
420 425 430
His Leu Lys Asp Ser Gly Ala Ser Thr Asp Asp Ser Ala Ala Glu Lys
435 440 445
Lys Gly Gly Thr Leu His Ala Gly Leu Ile Val Gly Ile Leu Ile Leu
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Val Leu Ile Ile Ala Ala Ala Ile Leu Val Thr Val Tyr Met Tyr His
465 470 475 480
His Pro Thr Ser Ala Ala Ser Ile Phe Phe Ile Glu Arg Arg Pro Ser
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35 40 45
Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr Phe Val
50 55 60
Glu Gln Leu Ala His Arg Phe Ile Ser Pro Gln Leu Arg Met Ser Phe
65 70 75 80
Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr Glu Asp
85 90 95
Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val Leu Pro
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Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser Glu Gln
115 120 125
Ile Tyr Tyr Glu Asn Ser Gln Gly Tyr Arg Thr Ala Ser Val Ile Ile
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Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr Ser Glu
145 150 155 160
Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr Cys Val
165 170 175
Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala Asp Ser
180 185 190
Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu Gln Gly
195 200 205
Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu Ala Ala
210 215 220
Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val Val Arg
225 230 235 240
Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu Cys Ser
245 250 255
Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe Ala Val
260 265 270
Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu Val Gly
275 280 285
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290 295 300
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305 310 315 320

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355 360 365
Pro Lys Lys Lys Trp Pro Thr Val Asp Ala Ser Tyr Tyr Gly Gly Arg
370 375 380
Gly Val Gly Gly Ile Lys Arg Met Glu Val Arg Trp Gly Glu Lys Gly
385 390 395 400
Ser Thr Glu Glu Gly Ala Lys Leu Glu Lys Ala Lys Asn Ala Arg Val
405 410 415
Lys Met Pro Glu Gln Glu Tyr Glu Phe Pro Glu Pro Arg Asn Leu Asn
420 425 430
Asn Asn Met Arg Arg Pro Ser Ser Pro Arg Lys Trp Tyr Ser Pro Ile
435 440 445
Lys Gly Lys Leu Asp Ala Leu Trp Val Leu Leu Arg Lys Gly Tyr Asp
450 455 460
Arg Val Ser Val Met Arg Pro Gln Pro Gly Asp Thr Gly Arg Cys Ile
465 470 475 480
Asn Phe Thr Arg Val Lys Asn Ser Gln Pro Ala Lys Tyr Pro Leu Asn
485 490 495
Asn Thr Tyr His Pro Ser Ser Pro Pro Pro Ala Pro Ile Tyr Thr Pro
500 505 510
Pro Pro Pro Ala Pro His Cys Pro Pro Pro Ala Pro Ser Ala Pro Thr
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Ser Val

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PEM's
complete web table #25 (PEM3) + #47 (PEM6) are G1, rest are G3

Table 1. Previously characterized and novel Pan Endothelial Markers. The most abundant tags derived by summing the tags from Normal EC (N-EC's) and Tumor EC (T-EC's) SAGE libraries are listed in descending order. N-EC and T-EC SAGE libraries contained 96,694 and 96,688 SAGE tags respectively. For comparison, the corresponding number of SAGE tags found in cultured human umbilical vein endothelial cells (HUVEC), human dermal microvascular endothelial cells (HMVEC), and non-endothelial cell lines (Cell Lines) are shown. The HUVEC SAGE library contained 290,000 tags and the HMVEC library 111,000 tags. Non-endothelial cell lines consisted of 1.8×10^{6} tags derived from a total of 14 different cancer cell lines including colon, breast, lung, and pancreatic cancers, as well as one non-transformed keratinocyte cell line, two kidney epithelial cell lines, and normal monocytes. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. The sequence CATG precedes all tags and the 15th base (11th shown) was determined as previously described by Velculescu et. al. (Nat Genet 1999 Dec;23(4):387-8).

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	CATATCATTAA	247	501	130	87	2	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
2	TGCACTTCAAG	328	141	0	0	0	hevin
3	TTTGCACCTTT	165	84	191	115	4	connective tissue growth factor (CTGF, IGFBP-rP2)
4	CCCTTGTCCG	131	104	1	1	0	ESTs
5	TTGCTGACTTT	73	131	2	14	1	collagen, type VI, alpha 1
6	ACCATTGGATT	102	67	0	0	2	interferon induced transmembrane protein 1 (9-27, Leu 13)
7	ACACTTCTTTC	104	44	60	62	2	guanine nucleotide binding protein 11
8	TTCTGCTCTTG	71	67	118	72	0	von Willebrand factor
9	TCCCTGGCAGA	68	68	3	13	3	cysteine-rich protein 2 (CRP-2, ESP-1, SmLIM)
10	TAATCCTCAAG	26	108	34	16	1	collagen, type XVIII, alpha 1
11	ATGTCTTTTCT	58	65	17	17	3	insulin-like growth factor-binding protein 4
12	GGGATTAAAGC	40	67	30	14	2	CD146 (S-Endo 1, P1H12, Muc18, MCAM, Mel-CAM)
13	TTAGTGTCGTA	38	69	9	13	0	SPARC (osteonectin, BM-40)
14	TTCTCCCAAAT	20	86	16	64	2	collagen, type IV, alpha 2
15	GTGCTAAGCGG	24	74	0	10	2	collagen, type VI, alpha 2
16	GTTTATGGATA	35	56	11	11	1	matrix Gla protein (MGP)
17	CCCTTTCACAC	52	33	0	0	0	ESTs, Weakly similar to HPBRII-7 protein
18	TGTTCTGGAGA	58	27	18	56	2	gap junction protein, alpha 1, 43kD (connexin 43)
19	AAGATCAAGAT	34	50	2	4	1	actin, alpha 1, skeletal muscle / actin, alpha 2, smooth muscle, aorta
20	TCTCTGAGCAT	32	48	0	0	0	aggrecanase 1 (metalloproteinase with thrombospondin type 1 motifs, 4)
21	CAGGTTTCATA	22	56	0	0	0	small inducible cytokine subfamily B (Cys-X-Cys), member 14 (BRAK)
22	GCACAAGTTCT	43	25	6	22	0	calcitonin receptor-like receptor activity modifying protein 2
23	AGCTTGTGGCC	45	23	0	0	0	calcitonin receptor-like receptor activity modifying protein 3
24	CTTCTGGATAA	13	54	12	0	0	cell division cycle 42 (GTP-binding protein, 25kD)
G1 25	CAACAATAATA	42	25	13	6	0	ESTs

26	ACCGGCGCCCG	50	15	0	0	0	tetranectin (plasminogen-binding protein)
27	GGAAGCTAAGT	35	27	0	5	1	osteoblast specific factor 2 (fasciclin I-like)
28	GCAATTTAACC	38	21	0	3	0	solute carrier family 21 (prostaglandin transporter), member 2
29	GATAACTACAT	18	35	4	4	0	angiomodulin (ANG, IGFBP-7, IGFBP-rP1, Mac25, TAF)
30	TATGAGGGTAA	19	30	40	2	0	regulator of G-protein signalling 5
31	CCACGGGATTC	10	39	0	0	0	collagen, type III, alpha 1
32	TTTACAAAGAG	26	21	0	1	1	carboxypeptidase E
33	CCCAGTAAGAT	22	25	0	16	1	cysteine and glycine-rich protein 2 (LIM domain only, smooth muscle)
34	ACAAAGCATTT	26	20	0	14	1	Human insulin-like growth factor binding protein 5 (IGFBP5) mRNA
35	GCCTGTCCCTC	8	38	22	11	0	ESTs / biglycan
36	TACTTTATAAG	25	21	1	1	0	metalloproteinase with thrombospondin type 1 motifs (ADAMTS1, METH-1)
37	TGTTTAATACA	15	29	2	1	1	ESTs / erythrocyte membrane protein band 4.1-like 2
38	GTCCCTGCCTT	18	25	1	1	0	glutathione S-transferase M2 (muscle)
39	GAGCCATCATA	21	21	2	2	1	ESTs / GTP-binding protein overexpressed in skeletal muscle
40	GGCCCTACAGT	26	13	2	3	0	ESTs / KIAA0821 protein
41	GCTAACCCCTG	7	31	0	1	0	ESTs
42	ATCACACAGCT	19	18	0	0	0	thyroid and eye muscle autoantigen D1 (64kD)
43	ACAAGTACTGT	18	19	36	27	0	cadherin 5, VE-cadherin (vascular epithelium)
44	TCACCGTGGAC	20	17	0	1	0	selectin P (granule membrane protein 140kD, antigen CD62)
45	ACATTCCAAGT	18	18	0	1	1	tissue inhibitor of metalloproteinase 3
46	GAGCCTGGATA	6	29	0	0	0	chondroitin sulfate proteoglycan 4 (melanoma-associated)
G1 · 47	GGCACTCCTGT	22	13	19	12	0	ESTs
48	TCACAGCCCCC	20	15	8	5	0	ESTs
49	TGCCAGGTGCA	10	23	0	1	0	albumin
50	TGGGAAACCTG	11	22	0	1	1	eukaryotic translation initiation factor 4 gamma, 1
51	TTTCATCCACT	20	13	0	2	0	ESTs, KIAA0362 protein
52	AACAGGGGCCA	15	18	0	0	1	interferon, alpha-inducible protein (clone IFI-6-16)
53	ACTGAAAGAAG	6	26	0	0	1	complement component 1, s subcomponent
54	ACCGTTCTGTA	8	24	10	6	0	transcription factor 4
55	ATACTATAATT	25	6	12	0	0	ESTs
56	TTTGTATAGAA	17	15	4	5	1	hect domain and RLD 2
57	GTAATGACAGA	20	11	1	1	1	stanniocalcin
58	AATAGGGGAAA	13	19	4	1	0	ESTs, KIAA1075 protein
59	GTGCTACTTCT	5	25	2	18	0	collagen, type IV, alpha 1
60	CCGGCCCCTCC	6	24	0	0	1	peanut (Drosophila)-like 2
61	TTGAATTTGTT	19	10	1	1	0	RNA-binding protein gene with multiple splicing
62	CGAGAGTGTGA	22	6	0	0	0	ESTs
63	CCCTGTTCAGC	14	15	38	24	0	tyrosine kinase with IgG and EGF homology domains (Tie)

64	CAGATGGAGGC	18	10	1	9	0	ESTs
65	AGGCTCCTGGC	8	20	0	0	0	ESTs
66	TCTGCTTCTAG	20	8	40	15	0	ESTs
67	GGCTTAGGATG	18	9	10	14	0	ESTs
68	GGTTGTTGCGG	6	21	0	0	1	ESTs
69	ACAAGTACCCA	5	22	4	5	0	P311 protein
70	CTTCTCTTGAG	18	9	1	4	1	basic transcription element binding protein 1
71	GCTAATAATGT	10	17	0	2	0	KIAA1077 protein
72	TGTGCTTTTTT	10	15	1	4	0	KIAA0758 protein / protein kinase, cAMP-dependent, catalytic, alpha
73	CATCACGGATC	17	8	0	1	0	interleukin 1 receptor, type I
74	GCAGCAGCAGC	6	18	0	2	0	T-box 2
75	TGACTGTATTA	13	11	0	0	0	ESTs / amine oxidase, copper containing 3 (vascular adhesion protein 1)
76	GAATGCTCTTG	6	18	0	11	0	gap junction protein, alpha 4, 37kD (connexin 37)
77	GTAGTTCTGGA	18	6	0	5	0	ESTs, clone 23698 mRNA
78	TCCCCTCTCTC	6	17	0	0	0	periodontal ligament fibroblast protein
79	GGGCAGTGGCT	5	18	12	5	0	ESTs, DKFZP586B0621 protein
80	AAATATGTGTT	19	4	13	3	0	ESTs
81	GTCATTTTCTA	11	11	10	2	0	transcription factor 8 (represses interleukin 2 expression)
82	CTCTCCAAACC	14	8	0	0	0	complement component 1 inhibitor (angioedema, hereditary)
83	TTAATGTGTAA	4	18	0	0	0	guanylate cyclase 1, soluble, beta 3
84	TCAAGCAATCA	13	9	0	1	0	ESTs
85	GAAGACACTTG	15	7	1	0	0	ESTs
86	GGGTAGGGTGA	6	15	0	0	1	integrin, alpha 7
87	TGGAACAGTGA	10	10	10	5	0	ESTs
88	GAGTGGCTACC	10	9	0	0	0	ESTs
89	GTCAGGGTCCC	13	7	0	9	0	decidual protein induced by progesterone
90	GTCAGTCACTT	14	8	4	1	0	hairy (Drosophila)-homolog
91	AGCAGAGACAA	14	8	1	10	0	natriuretic peptide receptor A - guanylate cyclase A
92	AGCGATGGAGA	9	10	0	0	0	ESTs
93	CGTGGGGTGTA	9	10	17	3	0	

TEM's complete web table

Table 2. SAGE tags elevated in tumor endothelium. The top 46 tags with the highest tumor EC (T-EC's) to normal EC (N-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis. †; multiple tags for this gene are due to alternative polyadenylation sites.

see table 2 from paper for G1, G2 or G3

all G3

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	GGGGCTGCCCA	0	28	0	2	0	ESTs, similarity to thrombomodulin TEM1
2	GATCTCCGTGT	0	25	0	0	0	ESTs, similarity to rat Rhes ras-related protein TEM2
3	CATTTTTATCT	0	23	0	0	0	ESTs
4	CTTTCTTTGAG	0	22	6	20	1	regulated in glioma-like 7-1 (Dkk-3/ REIC)
5	TATTAACTCTC	0	21	1	3	1	ESTs, similarity to JNK interacting protein-3a
6	CAGGAGACCCC	0	16	2	0	0	MMP-11 (stromelysin 3)
7	GGAAATGTCAA	1	31	53	22	1	MMP-2 (gelatinase A, 72kD type IV collagenease)
8	CCTGGTTCAGT	0	15	0	0	0	ESTs
9	TTTTTAAGAAC	0	14	1	4	0	ESTs
10	TTTGGTTTTCC	5	139	0	16	0	collagen, type I, alpha 2, transcript A†
11	ATTTTGTATGA	0	13	4	8	0	nidogen (entactin)
12	ACTTTAGATGG	1	23	0	15	0	collagen, type VI, alpha 3
13	GAGTGAGACCC	3	63	0	0	1	Thy-1 cell surface antigen
14	GTACACACACC	0	10	0	0	0	ESTs / cystatin S
15	CCACAGGGGAT	2	38	0	2	1	collagen, type III, alpha 1
16	TTAAAAGTCAC	1	19	1	3	1	ESTs
17	ACAGACTGTTA	4	74	0	0	0	ESTs, similarity with sea squirt nidogen TEM7
18	CCACTGCAACC	1	18	0	1	0	
19	CTATAGGAGAC	1	18	1	1	0	ESTs, similarity with homeobox protein DLX-3 TEM8
20	GTTCCACAGAA	0	9	0	3	0	collagen, type I, alpha 2, transcript B†
21	TACCACCTCCC	0	9	4	1	1	ESTs / pregnancy specific beta-1-glycoprotein 1
22	GCCCTTTCTCT	1	17	3	1	2	endo180 lectin
23	TTAAATAGCAC	2	33	0	4	0	collagen, type I, alpha 1
24	AGACATACTGA	1	16	1	0	0	ESTs, DKFZP434G162 protein
25	TCCCCCAGGAG	1	16	0	0	0	bone morphogenetic protein 1 (metalloprotease)
26	AGCCCAAAGTG	0	8	0	0	0	
27	ACTACCATAAC	0	8	0	0	0	slit (Drosophila) homolog 3 (MEGF5)
28	TACAAATCGTT	0	8	0	0	0	KIAA0672 gene product

G3

29	TTGGGTGAAAA	0	8	0	0	0	ESTs
30	CATTATCCAAA	0	8	0	0	0	integrin, alpha 1
31	AGAAACCACGG	0	8	2	7	0	collagen, type IV, alpha 1
32	ACCAAAACCAC	0	8	0	3	0	
33	TGAAATAAAC	0	8	3	1	1	
34	TTTGGTTTCC	1	15	0	0	0	ESTs
35	GTGGAGACGGA	1	15	1	2	1	ESTs
36	TTTGTGTTGTA	1	14	2	0	0	collagen, typeXII, alpha 1
37	TTATGTTTAAT	3	39	0	0	1	lumican
38	TGGAAATGACC	15	179	0	40	0	ESTs / collagen, type I, alpha 1
39	TGCCACACAGT	1	13	0	2	0	transforming growth factor, beta 3
40	GATGAGGAGAC	3	35	0	18	1	collagen, type I, alpha 2, transcript C[†]
41	ATCAAAGGTTT	2	23	0	0	0	ESTs, DKFZp564O222 mRNA
42	AGTCACATAGT	1	11	2	0	0	cell division cycle 42 (GTP-binding protein)
43	TTCGGTTGGTC	4	45	0	19	0	
44	CCCCACACGGG	2	21	0	0	0	ESTs
45	GGCTTGCCTTT	1	10	0	10	1	
46	ATCCCTTCCCG	1	10	1	0	0	peanut-like protein 1

Table 3. Detection of transcripts in various tumor types by RT-PCR and in situ hybridization (ISH). The "+" sign indicates the presence of a robust RT-PCR product or stong positive staining of vessels by in situ hybridization. The "-" sign indicates an undetectable signal by in situ hybridization or an absent or barely detectable transcript by RT-PCR. The "+/-" sign indicates a very weak signal in a limited number vessels by in situ hybridization.

		TEM1	TEM3	TEM4	TEM5	TEM7	TEM8	TEM9	vWF	Hevin
RT-PCR	Colon Nor.	-	-	-	-	-	-	-	+	ND
	Colon Tum.	+	+	+	+	+	+	+	+	ND
ISH	Colon Nor.	-	-	-	-	-	-	-	+	+
	Colon Tum.	+	+	+	+	+	+	+	+	+
	Liver Met.	+	+/-	+	+	+	+	+	+/-	ND
	Lung Tum.	+	ND	+	+	+	+	+	+	+
	Brain Tum.	+	ND	ND	ND	+	ND	ND	+	+*
	Corpus Lut.	+	+	+	+	+	-	+	+	+
	Wound	+	ND	+	ND	+/-	+/-	ND	+	+

* hevin was localized to both endothelial cells and malignant cells in brain tissue.
ND: not determined.

www.sagenet.org\angio\table3.htm (to be posted upon publication)

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Table 9. SAGE tags elevated in normal endothelium. The top 46 tags with the highest normal EC (N-EC's) to tumor EC (T-EC's) tag ratios are listed in descending order. To calculate tag ratios, a value of 0.5 was assigned in cases where zero tags were observed. The SAGE libraries are the same as those listed in Table 1. Tag numbers for each group were normalized to 100,000 transcripts. A 'Description' of the gene product corresponding to each tag is given, followed by alternative names in parenthesis.

no.	Tag Sequence	N-EC's	T-EC's	HUVEC	HMVEC	Cell Lines	Description
1	TCTCACGTCT	26	0	0	0	0	mucosal vascular addressin cell adhesion molecule 1
2	CTAGCGTTTT	19	0	4	14	0	serum deprivation response (phosphatidylserine-binding protein)
3	GTGGCTGACG	18	0	1	0	0	ESTs / intercellular adhesion molecule 4
4	CTCTTAAAAA	34	1	1	0	0	small inducible cytokine subfamily A (Cys-Cys), member 14
5	TGGGAAGAGG	16	0	3	4	1	ESTs
6	GTTTAAGGAT	16	0	0	0	0	ESTs
7	CTTTGTTTTG	15	0	56	32	1	endothelin 1 / ribosomal protein L27
8	ATTGCCAATC	14	0	0	4	0	TU3A protein
9	TGTTGAAAAA	21	1	1	0	0	selectin E (endothelial adhesion molecule 1)
10	ACAAAAAGGC	21	1	0	6	0	TU3A protein
11	AAGATGCACAC	21	1	1	1	1	phosphodiesterase I - nucleotide pyrophosphatase 2 (autotaxin)
12	GTAGAGGAAA	10	0	0	9	0	platelet/endothelial cell adhesion molecule (CD31 antigen)
13	TTGTTCAAGG	10	0	0	1	0	ESTs
14	CTCTTCAAAAA	19	1	1	9	0	ESTs / small inducible cytokine subfamily A, member 14
15	TATTAAAATA	18	1	6	9	1	transforming growth factor, beta receptor II (70-80kD)
16	GAATTCACCA	9	0	1	14	0	ESTs
17	AAGGAGAACT	9	0	0	0	0	small inducible cytokine subfamily A, member 14
18	AATATCTGAC	9	0	2	2	2	active BCR-related gene
19	TCAGTGACCAG	17	1	4	7	2	protein kinase C eta
20	GCAAAGTGCC	32	2	1	5	0	ESTs
21	TAAATACTTG	8	0	2	0	0	ESTs (2 unigene clusters)
22	GTCACTAATT	8	0	1	0	0	ESTs
23	ATAACCTGCA	8	0	0	0	0	signaling lymphocytic activation molecule
24	TGCATCTGTGC	46	3	1	1	0	ESTs / glycogenin 2
25	TAAAGGCACA	15	1	4	3	0	LIM binding domain 2
26	GACCGCGGCT	73	5	11	7	0	claudin 5
27	ACTCCGGTGT	14	1	0	8	0	ESTs

28	CTTCTCACCT	27	2	3	1	0	GTP-binding protein
29	TCGTGCTTTG	13	1	0	0	0	ESTs
30	GAGCAGTGCT	13	1	4	2	1	feline sarcoma viral (v-fes) - Fujinami avian sarcoma viral (v-fps) homolog
31	CTCTAAAAAA	10	1	0	1	0	ESTs
32	GAAACCCGGT	10	1	0	0	1	phospholipase C, beta 4
33	AACACAGTGC	10	1	7	15	1	ESTs